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July, 1956

A Comparison of the Toxoplasmin Skin Tests, the Sabin-Feldman Dye Tests, and the Complement Fixation Tests for Toxoplasmosis in Various Forms of Uveitis. LEON JACOBS, HOWARD NAQUIN, RICHARD HOOVER AND ALAN C. WOODS 1

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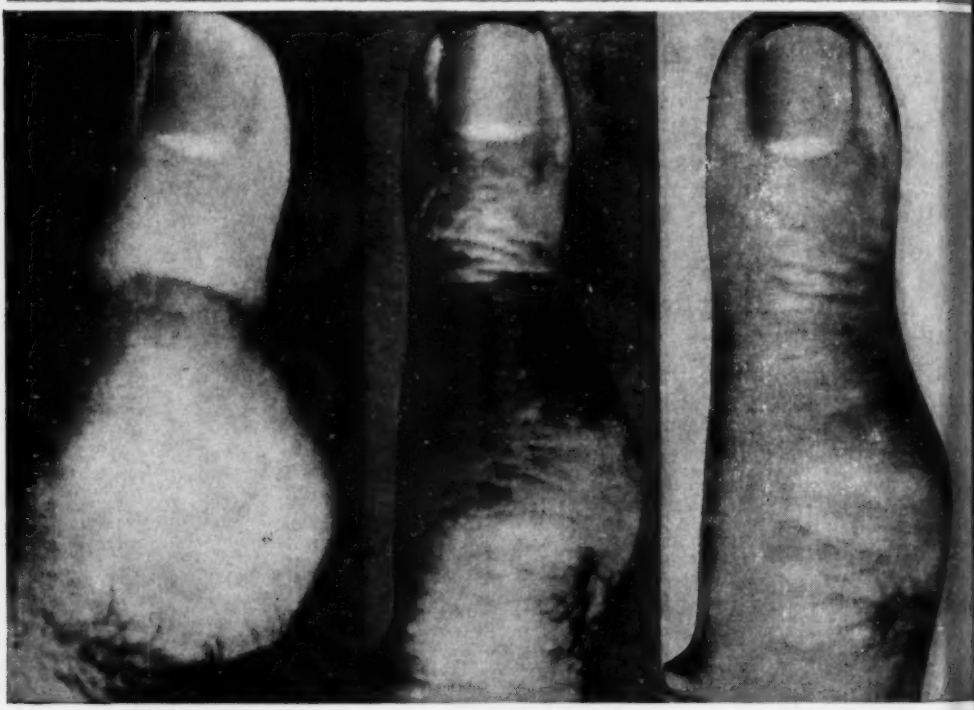

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A COMPARISON OF THE TOXOPLASMIN SKIN TESTS, THE SABIN-FELDMAN DYE TESTS, AND THE COMPLEMENT FIXATION TESTS FOR TOXOPLASMOSIS IN VARIOUS FORMS OF UVEITIS[1]

LEON JACOBS,[2] HOWARD NAQUIN,[3] RICHARD HOOVER,[3] AND ALAN C. WOODS[3]

Received for publication March 2, 1956

In October of 1953, in a communication from the Wilmer Institute and the National Microbiological Institute, the results of the Sabin-Feldman dye test for toxoplasmosis on 409 stored serums from various types of patients were reported (1). Ninety-eight of these serums were from patients without uveitis, 110 were from patients with non-granulomatous uveitis and 201 serums were from patients with granulomatous uveitis. The various uveitis patients had been carefully studied in the Wilmer Institute to determine, if possible, the causes of their uveitis, and their histories were available for analysis. The serums of patients either without uveitis or with non-granulomatous uveitis were used as controls. As a result of this study, subject to possible fallacies in the dye test, it was concluded that adult ocular toxoplasmosis was an actual clinical entity and was the factor responsible for the ocular disease in approximately 25 per cent of patients with granulomatous uveitis. It was further pointed out that a diagnosis of toxoplasmic chorioretinitis could be made only by correlation of the ocular picture, the results of a careful medical survey to exclude other possible causes, and the results of serologic tests for toxoplasmosis. At that time there were an insufficient number of cutaneous tests to evaluate results of the toxoplasmin skin test. The most frequent ocular lesion in the patient believed to have toxoplasmosis was a focal chorioretinitis. There were an appreciable number of cases of generalized uveitis and a few cases of retinal periphlebitis.

Since the publication of this paper, there have appeared a number of important reports on this subject of ocular toxoplasmosis, (2, 3, 4, 5, 6, 7, 8). *Toxoplasma gondii* has been demonstrated in the enucleated eyes of patients with chorioretinitis and uveitis, and the results of the skin and dye tests on these patients are known. As a result of these and various other studies, it is now generally conceded that acquired toxoplasmosis in an important cause of adult granulomatous uveal disease, and that the skin and dye tests are usually

[1] This work was supported in part by a grant from the National Institute of Neurological Diseases and Blindness.

[2] U. S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Institute of Allergy and Infectious Diseases, Laboratory of Tropical Diseases, Bethesda, Maryland.

[3] The Wilmer Ophthalmological Institute of the Johns Hopkins University and Hospital.

positive in these patients. However, while the evidence for these generalities is conclusive, nevertheless, in the individual clinical case, it is extremely difficult to evaluate the significance of the positive cutaneous and serologic tests, and there is no generally accepted criterion for a firm clinical diagnosis of acquired adult ocular toxoplasmosis. The difficulties arise from the relatively high incidence of positive results in apparently normal healthy individuals, the possible non-specificity of the dye test (9)[4], the improbability of isolating the parasite from the blood or extra-ocular tissues, and the absence of any associated systemic symptoms of infection with the parasite.

In the hope of resolving some of these difficulties, an analysis of the results of the toxoplasmin skin tests and of the serologic tests for toxoplasmosis has been made in 193 uveitis patients studied in the Wilmer Institute between July 15, 1953 and July 1, 1955. In all these patients, a diagnosis of either non-granulomatous or granulomatous uveitis was made on the first ophthalmologic examination. Patients in whom such a diagnosis could not be made are not included in this study. Eighty-six patients were thus diagnosed as having non-granulomatous uveitis believed due to an allergic insult, and 107 were diagnosed as having granulomatous uveitis believed due to an infection of the uveal tract with some pathogenic agent causing granulomatous disease. Many of the patients with non-granulomatous uveitis were in periods of remission between attacks, and the eyes were quiet. Practically all patients with granulomatous uveitis were in the active stages of the ocular disease. There was no particular difference in the age distribution of the patients with non-granulomatous uveitis and those with various types of granulomatous disease. The age distribution of these patients is shown in Table I. While these 193 patients showed a wide geographic distribution in their residences, nevertheless, the majority of them lived somewhere on the Atlantic seaboard.

All patients were subjected to a careful and extensive medical study to determine, if possible, the specific cause of the ocular disease. An attempt was made to ascertain, in the case of non-granulomatous uveitis, the specific bacterial hypersensitivity responsible for the allergic reaction; and in the case of uveitis, any evidence of systemic granulomatous disease which could cause the granulomatous ocular inflammation. The details of this medical survey have been outlined elsewhere (10). Included in this survey were intracutaneous tests with toxoplasmin, and Sabin-Feldman dye tests on the serums. In about 50 per cent of the serums, complement fixation reactions against a toxoplasma antigen prepared from mouse peritoneal exudates were done.[5] In the performance of these tests, to avoid anamnestic reactions, the usual pro-

[4] In the experience of one of us (L. J.), no confirmation of the reported cross-reactions has been obtained (11).

[5] The complement fixation tests were performed by the Immunology Subsection, Laboratory of Tropical Diseases, NIAID, NIH.

TABLE I

Age Distribution of Uveitis Cases

Type of uveitis	Total no. of cases	1–9 years	10–19 years	20–29 years	30–39 years	40–49 years	50–59 years	60 years +
Nongranulomatous	86	3 (4%)	10 (11%)	13 (15%)	22 (26%)	17 (20%)	16 (18%)	5 (6%)
Granulomatous of conventional or unknown etiology	58	0	5 (9%)	12 (21%)	14 (24%)	12 (21%)	9 (15%)	6 (10%)
Granulomatous—toxoplasma etiology	37	0	6 (16%)	7 (19%)	16 (43%)	7 (19%)	1 (3%)	0
Granulomatous—due either to toxoplasmosis or conventional causes	12	0	0	6 (50%)	3 (26%)	1 (8%)	1 (8%)	1 (8%)

cedure was first to draw the blood for the serologic tests and later do the toxoplasmin skin tests. The serologic studies were all made in the National Institute of Allergy and Infectious Diseases, and the skin tests and clinical studies were done in the Wilmer Institute. The intradermal antigen was prepared from mouse peritoneal exudates at the National Institute of Allergy and Infectious Diseases following the method of Frenkel (11). The skin tests were read on a 0 to 4-plus scale. A single + reaction indicates erythema of 5 to 7 mm with no or only slight induration; a ++ reaction erythema of 8 to 15 mm with some induration; a +++ reaction erythema of 15 to 25 mm with definite induration but without necrosis; and a ++++ reaction, an equally large erythema and induration and also some evidence of necrosis. The positive reactions were all of the delayed type, coming on 24 to 48 hours after the test injection.

In a preliminary review of the histories of these 193 patients, it was immediately apparent that the results of the dye tests in the non-granulomatous group of patients were almost exactly the same as those found in the control cases of the first series. Since there was no question of a possible toxoplasmic etiology in the patients with an uncomplicated non-granulomatous uveitis, the results of these diagnostic tests for toxoplasmosis in the non-granulomatous uveitis group were again used as controls for the evaluation of the results of these same tests in the granulomatous uveitis group.

When the case histories of the patients with granulomatous uveitis were reviewed in the light of the results of the medical survey, and our former idea of the proper interpretation of the diagnostic tests for toxoplasmosis, they could readily be divided into four general groups. These were: *A*. Patients in whom the uveitis appeared clearly attributable to one of the conventional etiologies; *B*. Patients in whom positive tests for toxoplasmosis offered the only evidence for an etiologic diagnosis; *C*. Patients in whom there was evi-

dence of a conventional etiology which could explain the uveitis, and also evidence of toxoplasma infection, thus raising the question of alternative diagnosis; and *D*. Patients in whom the diagnostic survey had not revealed sufficient evidence of any granulomatous disease to justify an etiological diagnosis.

When the case histories of the patients in whom positive tests for toxoplasmosis offered the only explanation of the uveitis were further reviewed, it was found they all fulfilled each of the following criteria: (1) They showed an ocular picture believed to be compatible with ocular toxoplasmosis, i.e. a focal chorioretinitis, old glial scars with a superimposed acute allergic reaction, a generalized granulomatous uveitis, or (in the first series) a retinal periphlebitis. (2) All patients showed a positive skin test to toxoplasmosis. All patients (except one) showed positive dye tests in a minimum titer of 1:64. This exception was a child of 10 years who had a non-granulomatous uveitis superimposed on old glial scars. In this patient the skin test was +++ and the dye test was 1:16. (3) In none of these patients was there any evidence of other granulomatous disease to which the uveitis could logically be attributed.

These three criteria were then adopted as the requisites for a diagnosis of ocular toxoplasmosis in the individual case and the case histories of the patients with granulomatous uveitis were again reviewed. Final diagnosis of either conventional etiology, ocular toxoplasmosis, uncertain etiology, or undetermined etiology were then made and the patients rearranged in these four groups. The results of the various diagnostic tests for toxoplasmosis in the control group and in these various types of granulomatous uveitis are given below.

RESULTS

Incidence of Positive Skin and Dye Tests. The results of the cutaneous tests with toxoplasmin and the dye tests on the serums of the patients with the two types of uveitis are shown in Table II. Thus, in non-granulomatous uveitis the total incidence of positive skin tests was 27 per cent and of positive dye tests was 20 per cent. Both tests were positive in 14 per cent of these patients. In contrast, in the granulomatous uveitis group, 61 per cent of the patients showed positive skin tests, 62 per cent showed positive dye tests, and both tests were positive in 54 per cent. These figures are quite comparable to the results previously reported in the first series of stored serums from uveitis patients.

Etiological Diagnosis. The number of patients in the four etiological groups of granulomatous uveitis and their percentage incidence are shown in Table III. For comparison, the results of the etiological study on the patients in the first series are also shown. It must, however, be remembered that in the first series the diagnoses of ocular toxoplasmosis were all tentative and were based on the

TABLE II

Results of Skin and Dye Tests in Different Types of Uveitis

Type of uveitis	Total no. of cases	No. and incidence of positive skn tests	No. and incidence of positive dye tests	No. and incidence of skin and dye tests positive
Non-granulomatous	86	26 or 30%	17 or 20%	10 or 14%
Granulomatous	107	65 or 61%	67 or 62%	58 or 54%

TABLE III

Probable Incidence of Adult Toxoplasmosis in Etiology of Granulomatous Uveitis

Material studied	No. of cases	Final etiological diagnosis			
		Conventional causes	Adult toxoplasmosis	Uncertain etiology (conventional causes or toxoplasmosis)	Undetermined
Preserved serums from previously studied patients	191	80 or 42%	42 or 22%	35 or 18%	34 or 18%
Serums from patients under active study	107	29 or 27%	37 or 35%	12 or 11%	29 or 27%
Totals	298	109 or 37%	79 or 26%	47 or 16%	63 or 21%

delayed results found in the stored serums and on the previous medical surveys.

In the conventional etiology group, there were 29 patients, an incidence of 27 per cent as compared to an incidence of 42 per cent in the first series. This drop is undoubtedly partly due to the introduction of the therapeutic trial test for ocular tuberculosis and partly to stricter diagnostic criteria adopted for the diagnosis of other granulomatous disease entities as the etiologic factors. Only one patient in this group showed both skin and dye tests for toxoplasmosis positive. In this patient, the skin test was ++ and the dye test positive in a titer of 1:64. Despite these positive findings, the other evidence in favor of a tubercular etiology was considered more convincing.

The number of cases ascribed to ocular toxoplasmosis was 37, an incidence of 35 per cent. The reason for this increase is not apparent.

The uncertain etiology group dropped from 18 per cent incidence in the first series to 11 per cent on this series. This may well be due to the stricter criteria mentioned above. These same factors would also account for the rise in the undetermined etiology group from 18 to 27 per cent.

The cases attributed either to toxoplasmosis, or to uncertain etiology (conventional causes or toxoplasmosis) comprise 46 per cent of the patients with granulomatous uveitis. How great is the possible error as concerns a toxoplasmic etiology in these two groups? The question is difficult to answer, but since there was a 14 to 27 per cent incidence of positive tests in the control

TABLE IV

Relation of Toxoplasmin and Dye Tests to Complement Fixation Reaction

Result of toxoplasmin and dye tests	No. of cases	Complement fixation	
		Positive	Negative
Positive toxoplasmin + positive dye	38	7 or 18%	31 or 82%
Negative toxoplasmin + negative dye	23	0	23 or 100%
Positive toxoplasmin + negative dye	15	0	15 or 100%
Negative toxoplasmin + positive dye	16	0	16 or 100%

group of non-granulomatous uveitis patients, an equally large percentage of unrelated positive tests might be expected in the patients with granulomatous uveitis. The actual identity of such unrelated positive tests in granulomatous uveitis cannot be determined from the present information.

Value of Complement Fixation Reaction. Complement fixation reactions were done in 92 of the 193 patients. In 30 patients with non-granulomatous uveitis, the complement fixation test was negative in all, although in three of these patients both the skin and dye tests were positive. In 62 patients with granulomatous uveitis in whom the complement fixation test was done, it was positive in only 7 instances. In each of the 7 positive reactions both the skin and dye tests were also positive. However, the complement fixation reaction was positive in only 18 per cent of the 38 patients with both skin and dye tests positive in whom the test was done. Five of these 7 cases had an active exudative chorioretinitis which was ascribed to adult toxoplasmosis; the sixth patient had a chronic granulomatous uveitis believed due to toxoplasmosis, while in the seventh patient with a positive complement fixation reaction, the diagnosis lay between a tuberculous or toxoplasmic uveitis. The results of these 92 complement fixation reactions in relation to the results of the skin and dye tests are shown in Table IV.

From these figures it is evident that the complement fixation reaction is of little diagnostic aid in ophthalmic cases. The reaction is quite irregular in its appearance, and apparently does not remain positive for any prolonged period. A positive complement fixation reaction developing and increasing in titer during the progress of an acute infection is, of course, strong evidence for a toxoplasmic etiology. However, in this and in the previous series of patients, such a developing and increasing complement fixation reaction was observed in only two instances. Certainly, a negative test has no significance.

COMMENT

There are a number of interesting questions pertinent to these diagnostic tests which can be at least partially answered by the information available from this study. One of the first questions relates to the specificity of the skin and dye tests. A study of the cutaneous sensitivity to toxoplasmin showed no evi-

dence of any relation between this and positive reactions to tuberculin, brucellin, brucellergia, streptococcal, or other bacterial antigens to which the patients were tested. Likewise there was no relation between sensitivity to toxoplasmin and to any of the fungus antigens. As concerns both the skin and dye tests, no relation was found between positive reactions to these and any findings in the medical survey—skull calcification, eosinophilia, serum globulin, foci of infection, etc.

Further questions relate to the diagnostic criteria employed. Are they so strict that true cases of ocular toxoplasmosis are excluded from proper classification or are they so low that old and unrelated systemic *Toxoplasma* infections are incorrectly supposed to be the etiological factor in uveitis?

In answer to this question, it might be pointed out that in the case reported by Jacobs *et al.* (6) where the dye test was done at roughly the same time the *Toxoplasma* parasite was demonstrated in the ocular lesion, the titer was 1:64. In the case of Duke-Elder *et al.* (5) when the dye test was done 21 months after the demonstration of the *Toxoplasma* in the eye, the titer was 1:160. In the series of 21 patients reported by Jacobs, Cook, and Wilder (2) in whose enucleated eyes Wilder had previously found the bodies typical or suggestive of *Toxoplasma*, there were dye tests as low as 1:32 two months after the enucleation of the eye. In two patients when the dye tests were done two and eight years after the enucleations, the tests were positive in titers of only 1:4 and 1:2 respectively, while in the other patients where the dye tests were done from one to seven years after the enucleation, the titers varied from 1:16 to 1:2048. From these various figures, it is evident that the minimum standard for a significant dye test for an adult cannot be greater than 1:64. However, in view of the results reported by Jacobs, Cook, and Wilder should it be lower? It must be remembered that their figures were from patients in whom the dye tests were done some months after the active eye disease. The immediate question is what shall be the standard for patients with active ocular disease? This can be partially answered by reanalyzing the figures of the dye test titers in the patients here reported. If the requirement for a significant dye test is lowered to a titer of 1:32 while other criteria are maintained, three additional cases are added to the toxoplasmic etiology group. If lowered to 1:16, two other cases will be added. Thus, the incidence of uveitis attributed to toxoplasmosis would rise from 35% to 38 and 40 per cent, respectively.

If the criteria are further lowered by omitting the requirement for a positive toxoplasmin skin test and at the same time lowering the requirements for a positive dye test, the incidence for toxoplasmosis as the cause of granulomatous uveitis rises to 45 per cent and over with a proportionate drop in the undetermined etiology groups. If the requirement for a compatible clinical ocular picture is removed and evidence in favor of other recognized conventional etiologies is disregarded, the incidence of endogenous ocular disease which would

thus be ascribed to toxoplasmosis on the basis of a 1:64 dye test alone would reach the high figure of 62 per cent, and will soar to still higher levels if the 1:64 titer requirement is lowered. Such interpretations of the frequency of toxoplasmosis as the cause of adult uveitis must be at present regarded as overly enthusiastic. In view of the evidence that proven active ocular toxoplasmosis can occur with dye test titers as low as 1:64, it does not appear possible to raise the standard for a significant test to above this figure. The effect of lowering the standard for a positive dye test while maintaining other standards is insignificant. Therefore, until the situation is further clarified, if a diagnosis of adult ocular toxoplasmosis is to be made in any given case of active ocular disease, it would appear unwise to reduce the requirements for a significant dye test to below the present levels, or at least no lower than 1:32.

What is the relation or lack of relation of positive and negative dye tests? The incidence of correlation between the skin and dye tests in both non-granulomatous and granulomatous uveitis is shown in Table V. Thus, in non-granulomatous uveitis there is correlation, i.e., both tests positive or both tests negative, in 73 per cent of the cases, and in granulomatous uveitis similar correlation in 85 per cent of the cases—statistically comparable figures, with an overall correlation of 80 per cent.

In 20 per cent of the cases, there was no correlation; either the skin test was positive and the dye test negative, or *vice versa*. There were 23 such cases in the non-granulomatous group and 16 such cases in the granulomatous group. This is shown in Table VI. What is the significance of one test positive and the other negative? It is known that skin sensitivity develops later than serum antibodies, and this explanation might account for some of the discrepant results in individual patients if there were some evidence that the infection had been recently acquired. Not enough proven cases have been followed for a long enough period to allow general statements concerning the relative persistence of serum antibodies and skin reactivity. An individual positive test may conceivably be either an indication of a toxoplasma infection, or due to a cross reaction with some other infectious agent, or to some technical error. In any event, when the histories of the patients with such unrelated tests are examined, the positive test appears to be of little significance. In the 23 patients with

TABLE V

Uveitis Cases with Correlation Between Skin and Dye Tests

Type of uveitis	No. of cases	Positive skin and positive dye	Negative skin and negative dye	Total no. and % with correlation
Non-granulomatous	86	10	53	63 or 73%
Granulomatous	107	58	33	91 or 85%
Totals	193	68	86	154 or 80%

TABLE VI

Uveitis Cases without Correlation Between Skin and Dye Tests

Type of uveitis	No. of cases	Positive skin and negative dye	Negative skin and positive dye	Total no. and % without correlation
Non-granulomatous	86	16	7	23 or 27%
Granulomatous	107	7	9	16 or 15%
Total	193	23	16	39 or 20%

non-granulomatous uveitis who showed no correlation between skin and dye tests, there was no suggestion of a toxoplasmic etiology in any of them. The 16 cases of granulomatous uveitis with uncorrelated tests were distributed as follows: (1) Eight cases ascribed to conventional etiologies; (2) seven ascribed to undetermined etiology; (3) one case of granulomatous uveitis with a superimposed allergic reaction, ascribed to undetermined etiology.

This last case was a 26 year old man with a high degree of cutaneous hypersensitivity to toxoplasmin and the dye test positive only with the undiluted serum. There were no other findings to which the ocular inflammation could be attributed. The ocular picture was that of old discrete glial scars in the fundus with a superimposed allergic reaction, marked retinal and subretinal edema, but no actual exudate. This picture could well have been due to a toxoplasma pseudocyst rupturing in sensitized tissue—an explanation first offered by Frenkel (1954). Despite the suspicion that the ocular disease was related to toxoplasmosis, on account of the lack of correlation, the case was recorded as of undetermined etiology.

The fact that there was an overall correlation between the skin and dye tests (both tests positive or both negative) in 80 per cent of all the cases raises an interesting question. If the skin test is positive, what is the expectancy of a positive dye test? This question is of practical importance and is especially pertinent because the skin test is easy to do, the antigen is available from a commercial source,[6] and no special equipment is necessary. The skin test is therefore well within the range of diagnostic procedures readily done by the practicing ophthalmologist. On the other hand, the dye test is technically difficult, entails the necessity of keeping infected animals in the laboratory and is available to only comparatively few clinical ophthalmologists.

A further analysis of the material on which this report is based gives a reasonable answer to the above question. In this series as a whole (counting both non-granulomatous and granulomatous uveitis), there were 92 patients with positive skin tests (Table II). When the results of the dye tests found in these 92 patients are analyzed according to (A) the Wilmer Ophthalmological

[6] It is understood that Eli Lilly and Company, Indianapolis, Indiana makes this antigen and distributes it free of charge to physicians who request it directly.

Institute (1:64) standard for a significant dye test; (B) a minimum titer of 1:32; and (C) a minimum titer of 1:16, the result is as follows:

A. Incidence of positive dye tests (W.O.I. standard) in positive skin reactions 72%
B. Incidence of positive dye tests (1:32 titer standard) in positive skin reactions 76%
C. Incidence of positive dye tests (1:16 titer) in positive skin reactions 90%

If only patients with granulomatous uveitis are considered, the figures are even more impressive. There were 66 positive skin reactions in the granulomatous uveitis group. The incidence of positive dye tests on the above A, B, and C standards in these 66 patients was as follows:

A. Incidence of positive dye tests (1:64 standard) in positive skin reactors 85%
B. Incidence of positive dye tests (1:32 standard) in positive skin reactors 90%
C. Incidence of positive dye tests (1:16 standard) in positive skin reactors 95%

These figures indicate the toxoplasmin skin test is an excellent screening test. In granulomatous uveitis the margin of error varies from 5 to 15 per cent according to the standards used for a positive dye test.

If these figures are examined for the converse, i.e. the incidence of positive skin tests in patients with positive dye tests, the results are somewhat different. Thus, with different dye test standards, A, B, and C in the overall picture (both granulomatous and non-granulomatous uveitis) there will be an increasing number of positive dye tests, while the number of positive skin tests stays constant, thus giving a declining incidence of correlation.

A. Dye test positive in W.O.I. standards—skin test positive in 81%
B. Dye test positive in 1:32 minimum titer—skin test positive in 80%
C. Dye test positive in 1:16 minimum titer—skin test positive in 76%

If granulomatous uveitis patients only are considered, the incidence of positive skin tests in patients with positive dye tests is as follows:

A. Dye test positive in 1:64 standards—skin test positive in 85%
B. Dye test positive in 1:32 minimum standard—skin test positive in .. 84%
C. Dye test positive in 1:16 minimum standard—skin test positive in .. 78%

These figures are obviously only of academic interest. It is interesting, however, that Frenkel in his 1954 report examined his skin and dye test results in this manner and found an 87 per cent incidence of positive skin tests in his positive dye test patients, a figure identical with the findings reported here where the higher W.O.I. standard for significantly positive dye tests was used.

Another interesting question concerns the intensity of the skin and dye tests. Does the intensity of these reactions follow any definite pattern in the course of toxoplasma uveitis, and has it any clinical significance? In Tables VII and

TABLE VII

Intensity of Skin Tests in Various Types of Uveitis

Type of uveitis	No. of cases	+	++	+++	++++
Granulomatous of conventional etiology	1	0	1	0	0
Granulomatous of uncertain etiology	12	5	7	0	0
Granulomatous of undetermined etiology	15	6	9	0	0
Granulomatous attributed to presumed acute toxoplasmosis	24	1	13	7	3
Granulomatous attributed to presumed chronic toxoplasmosis	13	4	6	3	0
Non-granulomatous	26	8	11	5	2

TABLE VIII

Intensity of Positive Dye Tests in Patients with Various Forms of Uveitis

Type of uveitis	No. of cases	Less than 1:256	1:256	1:512
Granulomatous of conventional etiology	8	4	3	1
Granulomatous of uncertain etiology	12	7	2	3
Granulomatous of undetermined etiology	10	9	1	0
Granulomatous attributed to presumed acute toxoplasmosis	24	7	4	13
Granulomatous attributed to presumed chronic toxoplasmosis	13	6	4	3
Non-granulomatous	17	11	2	4

VIII an attempt has been made to divide the cases of supposed toxoplasma uveitis into acute and chronic types and to plot the intensity of the skin and dye tests in these two groups. Such division into acute and chronic cases is difficult and often arbitrary and unreliable. For example, shall a patient with old glial scars in the fundus and a superimposed allergic reaction around them be classified as acute or chronic? Moreover, if the cases are divided into too many groups, the number in each group is so small it is meaningless. Nevertheless, for what it may be worth, such an analysis has been made.

Table VII shows the distribution of the skin reactions of different intensities in these two groups and, for comparison, in various forms of uveitis not believed due to toxoplasmosis. In the supposed acute form of the disease, three or four plus skin reactions were present in 10 of 24 cases, an incidence of 41 per cent. In 13 cases of the chronic form of ocular toxoplasmosis and 12 cases of uncertain etiology (chronic toxoplasmosis or conventional etiology) there were three instances of this high sensitivity, an incidence of 12 per cent. In the 28 cases of granulomatous uveitis, believed due to causes other than toxoplasmosis, there were no instances of high sensitivity. However, in 26 control patients with non-granulomatous uveitis there were seven instances of high sensitivity, an incidence of 27 per cent. This degree of high reactivity might well be expected in any group of allergic individuals.

Similarly, as shown in Table VIII, dye tests of 1:250 or over were present in 17 of 24 cases of acute ocular toxoplasmosis, an incidence of 70 per cent. In 25 cases of granulomatous uveitis, believed due either to chronic toxoplasmosis or of uncertain etiology, there were 12 cases of high dye test titers, an incidence of 48 per cent, while in the 18 cases believed due to causes other than toxoplasmosis, there were 5 high titer dye tests, an incidence of 21 per cent. In the non-granulomatous control group, there were six cases of high titers, an incidence of 35 per cent. These figures are of little statistical significance, and are open to criticism on the basis of the classification of patients. However, they show an apparent higher incidence of strong skin tests and high titer dye tests in the group of patients supposed to have acute ocular toxoplasmosis. Thus they tend to confirm Frenkel's contention that there are two general patterns of ocular toxoplasmosis, each with a somewhat different type of immune response. There are: A. Acute infections, where the skin test may at first be absent or of low intensity, but soon becomes strongly positive. The dye test is usually positive in high titers; the complement fixation test is variable, but it may become positive and reach high titers. *B.* Chronic infections, when the toxoplasmin test is positive, but only of moderate intensity. The dye test is positive, often in low titers, and the complement fixation test is usually negative.

The types of ocular lesions which are believed to be due to ocular toxoplasmosis are shown in Table IX. The incidence of these lesions in the patients previously reported (Series I) is also shown in this Table. There is little difference in the two series. In the overall picture there are 79 cases believed to represent examples of adult ocular toxoplasmosis. Fifty-one of these, or 65 per cent, were cases of the socalled "focal" choroiditis or chorioretinitis. Seven, or 9 per cent, were cases of old granulomatous choroiditis with a super-imposed allergic reaction. Seventeen were cases of generalized uveitis, an incidence of 21 per cent. There were four cases of retinal periphlebitis in the first series and none in the second series, an overall incidence of 5 per cent. However, since July 1, 1955 several cases of retinal periphlebitis believed due to toxoplasmosis

TABLE IX

Ocular Lesions Observed in Cases Attributed to Toxoplasmosis

Type of lesion	No. of cases		Overall total
	Series I	Series II	
Focal chorioretinitis	28	23	51
Disseminated or focal chorioretinitis with superimposed allergic reaction	3	4	7
Generalized uveitis	7	10	17
Periphlebitis retinae	4	0	4
Totals	42	37	79

have been observed, and there is no reason to modify the opinion that ocular toxoplasmosis may occasionally manifest itself under this clinical picture.

The last question concerns the effect of treatment on ocular toxoplasmosis. On this point there is but little information to be gleaned from patients here reported. The majority of the patients diagnosed as ocular toxoplasmosis were referred cases, and while treatment was instituted or recommended in all, the majority of them returned to the referring physicians and accurate follow-up information has not been obtained in many instances. In some the period of observation after treatment is still too short to permit any conclusions. In all, there are 22 patients with various forms of uveal disease believed due to a toxoplasma infection who have been treated with pyrimethamine (Daraprim) and sulfadiazine, and on whom reasonably accurate information is available. This information is given in Table X.

Thirteen of these 22 patients showed a favorable response to this therapy in the sense that the inflammatory reaction was speedily controlled. In five of these there was little return of vision, due to macular involvement. In four there was moderate improvement, and in four the improvement was dramatic. In three other cases there was questionable improvement in the clinical picture, and in six the treatment was without effect. Frenkel and Friedlander (1952–53) have shown that the *Toxoplasma gondii* occurs in both proliferative and cyst forms, each with a somewhat different morphology. Eyles (13) reported that while the proliferative form of the parasite is vulnerable to therapeutic attack the encysted form is protected. It is possible that this may explain the variations in the therapeutic response. In infections with the proliferative form chemotherapy would be effective, while in the acute super-imposed allergic reaction believed due to the rupture of a pseudocyst in sensitized tissue, chemotherapy would be ineffective and desensitization would theoretically be the proper procedure to reduce the hypersensitive uvea to a non-reactive state. As sufficient toxoplasmin has become available, several patients in this last category have been placed on such desensitization with the toxoplasma antigen. It will, however, be some time before the efficacy of this therapeutic attack can be evaluated.

In the administration of Daraprim and sulfadiazine the therapeutic regimen

TABLE X

Results of Treatment of Ocular Toxoplasmosis with Daraprim and Sulfadiazine

Result	No. of cases	Excellent	Moderate	Fair	Systemic reactions
Definite improvement	13	4	4	5	Four minor—leucopenia (2) crystalluria (1) weight loss (1)
Questionable improvement	3	—	—	—	Four severe—agranulocytosis (2)
No improvement	6	—	—	—	dermatitis and pyrexia (2)

thus far followed has been the administration of 25 mgm. of Daraprim daily for the first three weeks. Thereafter the drug is administered in the same dosage every second day. Sulfadiazine is given in a total daily dosage of 2 gm. during the period of therapy. Therapy is continued for a minimum of six weeks, if possible, then continued or discontinued on the basis of the observed therapeutic response.

As indicated in Table X, there was a large percentage of untoward reactions under this therapy. Four patients in this series had severe reactions. One of these required several transfusions to recover from agranulocytosis. Two other patients had a severe dermatitis with pyrexia. Four other reactions were relatively insignificant.

SUMMARY AND CONCLUSIONS

1. An analysis of the results of the skin and dye tests for toxoplasmosis has been made in 193 adult patients with uveitis. Eighty-six of these patients had the non-granulomatous form of the disease and 107 had the granulomatous form. The diagnostic criteria employed for the diagnosis of ocular toxoplasmosis in the individual case were as follows:

A. An ocular picture believed compatible with Toxoplasma infection.

B. The exclusion of other systemic granulomatous infections which could serve as the etiological factors.

C. The presence of a positive toxoplasmin skin test together with a dye test positive in a minimum titer of 1:64.

2. Under these criteria 37 cases or 35 per cent of the 107 cases of granulomatous choroiditis were attributed to toxoplasmosis.

3. An analysis of the results of the complement fixation reaction indicated that this test was of little or no value unless it developed during the course of an acute infection.

4. Although the incidence of a positive diagnosis of ocular toxoplasmosis is not greatly affected by lowering the standards for a significant dye test to positive in titers of 1:32 or even to 1:16, the evidence available from this study indicates that a dye test titer of at least 1:64 may reasonably be expected in an individual with active ocular toxoplasmosis, and it is at present unwise to reduce the criteria for a significant test below this level.

5. In the overall picture, with the dye test considered as positive only at titers of 1:64 or higher, there was 80 per cent correlation between the skin and the dye tests, i.e. both tests were either positive or both were negative.

6. There was no correlation, on the 1:64 dye test titer basis, between skin and dye tests in 16 patients with granulomatous uveitis. If titers of 1:16 were considered positive, there were only 2 patients with granulomatous uveitis who had positive skin tests and in whom the dye tests were negative.

7. In the entire series, there was a 72 per cent incidence of positive dye tests among the patients who showed positive skin tests. When the standards for a positive dye test were lowered to 1:32 and to 1:16, this incidence rose respectively to 76 and 90 per cent.

8. When granulomatous cases only were considered this incidence of positive dye tests under the three standards (1:64, 1:32, and 1:16) in positive skin reactions was respectively 85 per cent, 90 per cent, and 95 per cent.

9. High intensity skin tests and high titer dye tests appeared to be more frequent in the acute forms of ocular toxoplasmosis, although the evidence of these points is inconclusive.

10. In this and the former series there was a total of 79 cases of ocular disease attributed to toxoplasmosis. These cases were divided as follows: 51 cases of focal choroiditis or chorioretinitis, 7 cases of old granulomatous chorioretinitis with a secondary acute allergic reaction superimposed, 17 cases of generalized uveitis, 4 cases of retinal periphlebitis.

11. The effect of treatment with Daraprim and sulfadiazine in 22 patients was analyzed. In 13 of these there was a definite therapeutic response. Severe side reactions occurred in four patients.

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THE ADRENAL CORTEX IN DIABETIC RETINOPATHY: URINARY 17-HYDROXYCORTICOSTEROID EXCRETION STUDIES[1]

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Suggestive evidence has been accumulating in recent years, implicating the functional capacity of the adrenal cortex, more precisely the zona fasciculata of this organ, in the pathogenesis of diabetic retinopathy. It was postulated (1) that diabetics without retinopathy possessed a zona fasciculata which was less active than in the normal, whereas, diabetics with retinopathy possessed an overactive one. Previous reports from this Institute (2, 3) have discussed this hypothesis which was based upon the following: a) general clinical observations (4, 5), b) changes in the status of the retinopathy by a decrease of either hypophyseal or adrenal function (6, 7, 8), c) histopathological evidence (1) showing a relative adrenal hypertrophy and increased lipid vacuolization of the zona fasciculata found at autopsy in diabetics with Kimmelstiel-Wilson renal involvement (9), and similar kidney lesions found postmortem in a patient who had received massive doses of cortisone and ACTH for an orbital pseudotumor (10), and d) the finding that 40 per cent of diabetics without retinopathy failed to respond by a significant eosinophile drop to an intramuscular dose of 25 mgs. of corticotropin, whereas retinopaths responded uniformly to this dose as did healthy normal controls (11). The experimental production of lesions resembling the Kimmelstiel-Wilson nephropathy in normal and diabetic rabbits by the administration of intramuscular cortisone (12, 2), in alloxan diabetic animals by ACTH given intramuscularly (2), and in a dog made diabetic for 5 years by the administration of anterior pituitary extract (13) added support to this theory. Increased blood levels of 17-hydroxycorticosteroids (17-OH-CS) in insulin coma have also been reported (14).

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[4] This project was initiated by Dr. Jonas S. Friedenwald, whose untimely death did not allow his participation in the writing of this manuscript.

In 1953, when a more reliable analytical procedure for measuring urinary 17-OH-CS became available (15), it was decided to test this hypothesis in a more direct manner. The results of these studies, measuring daily urinary 17-OH-CS excretions, diurnal variations in this excretion, and the recovery of a standard test dose of 17-hydroxycorticosterone (Compound F) in normal patients, and in diabetics with and without retinopathy are presented in this report.

METHODS

1. *24-Hour Urinary 17-OH-CS Excretions*

Urinary 17-OH-CS was measured by the method of Porter and Silber (16) as modified by Glenn and Nelson (15), with a few minor changes (17). Cortisone alcohol was used as the basic analytical standard. The patients were instructed to collect 24-hour urine specimens and store them under refrigeration, and to refrain from taking any medication, other than insulin, for at least 72 hours prior to the start of urine collection. The urines were brought in immediately after the end of the collection period. Aliquots of these specimens were stored at −20°C. until analyzed. Normal controls were derived from hospital personnel and the ward and clinic services of the Wilmer Institute. The majority of the diabetic subjects were on insulin therapy, but some were controlled by diet alone. In all groups there was a large age variation which did not appear to influence the results significantly. The diabetic patients were carefully examined under mydriasis and classified ophthalmoscopically into retinopaths and non-retinopaths. The degree of retinopathy varied in severity from one or two microaneurysms to retinitis proliferans.

2. *Diurnal Variations*

The diabetic patients and normal controls were instructed to collect their urines in three successive fractions (8 P.M. to 8 A.M., 8 A.M. to 2 P.M. and 2 P.M. to 8 P.M.) under the conditions described above.

3. *Excretion After a Test Dose of Compound F*

The normal controls and diabetic patients received 100 mgs. of compound F orally early in the morning and were instructed to collect three successive 24-hour specimens under the conditions stipulated above. This was discontinued when it was found that an adequate estimate of Compound F excretion was obtained in the first 24 hours subsequent to the oral test dose. All results were evaluated with cortisone alcohol as the analytical standard.

RESULTS

1. *24 Hour Urinary 17-OH-CS Excretions*

The 24-hour urinary 17-OH-CS excretions of 39 normal controls, 47 diabetic patients without retinopathy and 49 diabetic patients with retinopathy are summarized in Table I.

Although there was no significant difference in 17-OH-CS excretion when either of the diabetic groups was compared with the normal controls, there was a statistically higher excretion in the pooled retinopaths when compared with

TABLE I

Comparison of 24-Hour Urinary Excretion of 17-OH-CS by Normal Patients and Diabetics With and Without Retinopathy

	Normals		Diabetics			
			Without retinopathy		With retinopathy	
	Female	Male	Female	Male	Female	Male
Number of cases	16	23	28	19	32	17
Age range	20–66	17–84	32–73	27–74	35–73	36–76
Range (mgs. 17-OH-CS)	2.3–6.9	2.2–10.2	1.5–9.3	0.8–8.9	1.8–13.5	3.3–13.2
Mean 1 (mgs. 17-OH-CS)	4.7	6.5	5.2	4.7	6.4	6.6
S.D. of mean 1	1.55	2.32	1.93	2.33	2.29	2.21
Mean 2 (mgs. 17-OH-CS) (males and females pooled)	5.8		5.0		6.4	
S.D. of mean 2	2.22		2.04		2.21	

Pooled retinopaths vs. non-retinopaths	$P < 0.01$ ($t = 3.42$) (18)
Female retinopaths vs. female non-retinopaths	$P < 0.05$ ($t = 2.25$)
Male retinopaths vs. male non-retinopaths	$P < 0.05$ ($t = 2.47$)
Pooled retinopaths vs. pooled normals	$P > 0.05$ ($t = 1.42$)
Pooled non-retinopaths vs. pooled normals	$P > 0.05$ ($t = 1.78$)

the pooled non-retinopaths. The same statistical significance was obtained when males and females were analyzed separately.

The difference in mean values between males and females, particularly in normals and in diabetics without retinopathy, should also be noted. An examination of the range of values observed in each of the three groups reveals that there was a large variation in the daily 17-OH-CS excretion among individuals.

The daily urinary excretion of three male patients, one normal (age 57), one patient without retinopathy (age 74), and one patient with retinopathy (age 47) was measured for several successive days. The results of this study are shown in Figure 1.

As can be seen, there was a large fluctuation in daily 17-OH-CS output, especially in the retinopath. But in spite of this large fluctuation, the comparison of the mean values between the diabetic with retinopathy and the normal control as well as the diabetic without retinopathy was statistically significant. The difference in 17-OH-CS output between the normal control and the diabetic without retinopathy was not statistically significant. For the normal control compared with the retinopath, $t = 6.03$ ($P < 0.01$); for the non-retinopath compared with the retinopath, $t = 5.35$ ($P < 0.01$).

2. *Diurnal Variation in Urinary 17-OH-CS Output*

In previous studies from this Institute (19) on diurnal endogenous eosinophile fluctuations, it was found that diabetics with retinopathy usually showed an afternoon depression in their eosinophile levels, in contrast to Halberg's findings for normals (20), who showed the lowest eosinophile counts during the

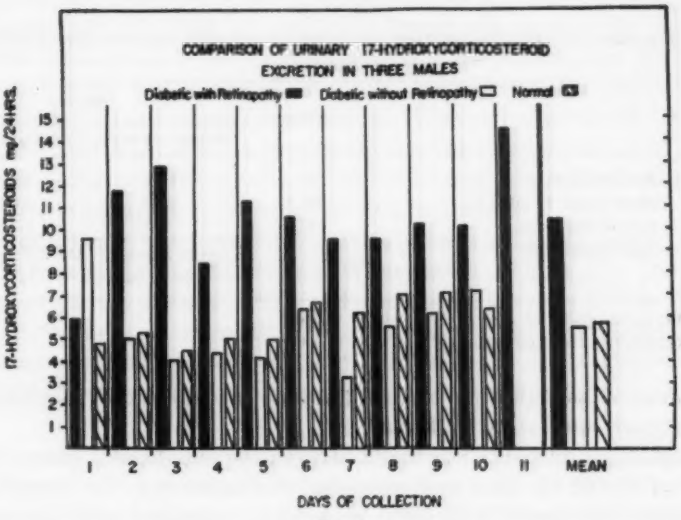
COMPARISON OF URINARY 17-HYDROXYCORTICOSTEROID EXCRETION IN THREE MALES
Diabetic with Retinopathy
Diabetic without Retinopathy
Normal
17-HYDROXYCORTICOSTEROIDS mg/24 HRS.
1 2 3 4 5 6 7 8 9 10 11 MEAN
DAYS OF COLLECTION

FIG. 1

TABLE II

Diurnal Variation in 17-OH-CS Excretion

Time period	Normal controls		Diabetics			
			Without retinopathy		With retinopathy	
	Mean mgs./hr	% of total 24 hrs.	Mean mgs./hr.	% of total 24 hrs.	Mean mgs./hr.	% of total 24 hrs.
8:00 P.M.–8:00 A.M.....	0.20	32	0.16	34	0.14	27
8:00 A.M.–2:00 P.M.....	0.56	44	0.43	46	0.49	47
2:00 P.M.–8:00 P.M.....	0.30	24	0.19	20	0.27	26

early morning hours. Diabetics without retinopathy often did not show any endogenous eosinophile fluctuations. To see if this might be reflected in adrenal activity, the diurnal variation of urinary 17-OH-CS output by diabetics with and without retinopathy was studied and compared with normal controls. The results of this study are summarized in Table II.

These results show no difference in the diurnal pattern within the three groups studied. In accordance with other reports (21), approximately 50 per cent of the daily 17-OH-CS output in each of the three groups was found in the period from 8 A. M. to 2 P. M.

3. *Excretion After a Standard Test Dose of Compound F*

It was thought that possibly a partially masked hyper- or hypo-metabolic activity for steroids in the diabetic subjects might be discovered by checking

TABLE III

Urinary Excretion of 17-OH-CS in the First Twenty-Four Hours After Administration of 100 mgs. of Compound F

	Normals	Diabetics	
		Without retinopathy	With retinopathy
Number of cases	9	13	13
Mean (mgs. 17-OH-CS)	39.6	25.3	33.7
S.D. of the mean	8.75	9.71	12.42
Diabetics pooled		Mean 2 (mgs. 17-OH-CS) 29.5	
		S.D. of Mean 2 11.1	

Normals vs. all diabetics $P < 0.02$ ($t = 2.48$)
Retinopaths vs. non-retinopaths $P > 0.05$ ($t = 1.92$)

the recovery of an orally administered test dose of compound F. The results of this study are summarized in Table III.

No significant difference was found between the two diabetic groups in excretion of 17-OH-CS after oral compound F. The recovery for compound F was significantly lower in diabetics as a whole compared with the normal controls. Again a very large range of excretion values, expressed in the standard deviation of the mean in Table III, was found, especially in the retinopathy group, so that it might be possible to reach a statistically valid conclusion for any difference between the two diabetic groups with a sufficiently large number of patients.

DISCUSSION

The results of this survey of urinary excretion of 17-OH-CS offer neither a contradiction to the adrenal hypothesis as one of the causal factors for the occurrence of diabetic retinopathy, nor do these studies afford definite proof of this theory. Should the diabetic with retinopathy excrete a considerable amount of 17-OH-CS as the sulfate ester, this would have escaped out observation, as our studies were limited to free 17-OH-CS appearing in the urine and to the glucuronide esters of these compounds. We have found a significantly higher urinary output of 17-OH-CS by the retinopaths when compared with nonretinopaths. The diabetics as a whole excrete a significantly smaller fraction of an oral test dose of compound F than do normal controls. Therefore, the increased 17-OH-CS excretion by the retinopaths might be attributed to an increased production of compound F by the adrenal gland. However, the high values found by no means approach the hyperactivity connected with Cushing's syndrome, nor is the low excretion any indication of Addison's disease. Diabetics respond to ACTH in a perfectly normal manner (22).

Steroids which are more polar than compound F would not have been extracted with chloroform, or if partially extracted would have been washed out

during the analytical purification procedure. An abnormal steroid produced by the diabetic adrenal would not have been found, and many of the metabolic products of compound F were not studied. It is also possible that the pattern established might be due to a difference in pituitary hormone production, or even pituitary functional capacity. Studies of blood levels of 17-OH-CS would only give information about a momentary state of function and could not resolve the diurnal production problem. The solution of this problem will have to await further advances in the study of adrenal function.

Several investigators have shown that a close relationship exists between diabetic retinopathy and Kimmelstiel-Wilson lesions (23, 24, 25). The microaneurysms of the diabetic retina and the microaneurysms of the diabetic glomerular vessels, characteristic of the early stages of the disease, are probably the primary vascular lesions, and might be indicative of an abnormality in mucoid metabolism. This hypothesis is currently being investigated.

SUMMARY

1. Diabetic patients with retinopathy excrete a significantly larger amount of urinary 17-hydroxycorticosteroids in 24 hours than diabetic patients without retinopathy. There is no significant difference between either diabetic group and the normal controls.

2. There is no difference in the urinary diurnal 17-OH-CS excretion pattern among the three groups.

3. The diabetic group as a whole shows a significantly smaller urinary 17-OH-CS excretion after an oral test dose of compound F than do normal controls.

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JONAS S. FRIEDENWALD: IN MEMORIAM[1]

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It is impossible to evaluate the great contribution of Jonas Stein Friedenwald to ophthalmology by a mere review of his scientific investigations and an enumeration of his achievements, writings, and the honors conferred on him. Outstanding and great as all these were, they were only parts of this many-faceted, yet singularly simple personality. Not only his scientific achievements, but also his life and his character have left their indelible mark on medicine, on ophthalmology, and on all those who were privileged to know him and to work with him.

Born in Baltimore in 1897, the son of Dr. Harry Friedenwald, who was himself a distinguished ophthalmologist, scholar and historian, Jonas was by birth a member of a proud and distinguished Jewish family, one dedicated to science and letters, with a devotion to their ancient traditions, a great pride in their race and lineage, a high feeling of "noblesse oblige", and a stalwart sense of personal honor and integrity. All of these qualities Jonas inherited. They were as much a part of him as the air he breathed. They guided him and influenced him throughout his entire life and they moulded his career as a citizen and a scientist.

[1] On February 10, 1956, at 5 P.M., the friends of Doctor Jonas Stein Friedenwald held a service in his memory in the Great Hall of the Welch Library. Dr. Friedenwald's interest extended beyond the field of science into art, music, and social welfare. It was not for these accomplishments alone, however, that his many friends gathered to pay tribute to him but because in his sincere, dedicated, unhurried way he had stimulated many of them to enter and pursue their own careers.

Three of Dr. Friedenwald's distinguished friends were asked to speak of his accomplishments and of his personality as they had known him. Dr. Alan C. Woods, Emeritus Professor of Ophthalmology of The Johns Hopkins University School of Medicine, had been Dr. Friedenwald's boyhood friend and his associate for thirty-two years. He described with deep warmth their close relations during these years and Dr. Friedenwald's accomplishments in the field of science. Honorable Justice Felix Frankfurter, Judge of the Supreme Court of the United States, spoke next of Dr. Friedenwald's interest in promoting an exchange of ideas between the specialities of law and medicine. Justice Frankfurter gave a vivid description of Dr. Friedenwald and his interest in law. Dr. Abel Wolman, Professor of Sanitary Engineering of The Johns Hopkins University, spoke of another facet of Dr. Friedenwald's life. He told with great sincerity of the tremendous influence that Dr. Friedenwald had had in the founding and development of the Hadassah Medical School and Hospital in Israel.

This meeting did not serve to bemoan the loss of Dr. Jonas Friedenwald so much, as it did to rejoin a sympathetic, kind, and tremendously capable friend. There were few people in the audience who had previously known of the extent of Dr. Friedenwald's varied accomplishments.

My acquaintance with Jonas dates from my early youth. I was some eight years older than he, and this is a considerable gap in childhood. Therefore I knew him only slightly in his early years. However, I have talked with many of his fellow-pupils of those early Calvert school days and they all describe a shy, proud, somewhat silent and reserved lad, with an alert and brilliant mind and a warm smile of appreciation for any minor attention shown him. This same retirement, modesty, intellectual brilliance, and appreciation of friendship characterized his later student days, in the Friends School, in the Johns Hopkins University, and in the Medical School where he graduated in 1920. After graduation in medicine, there followed a year of graduate training in internal medicine on the medical service of the Johns Hopkins Hospital. Then came a year's study of ophthalmic pathology under Dr. Verhoeff in Boston, and a final year's study under the preceptorship of Dr. de Schweinitz in Philadelphia. This was Jonas' formal training in ophthalmology—just two years preceptor training, but both under distinguished tutors. It is notable that he had no formal training in any of the special ophthalmic hospitals of that era. In the light of the present minimum requirements laid down by today's Specialty Boards, this was indeed scant preparation either for practice or for a scientific career. But when one considers that Jonas had been trained in ophthalmology in his home from his first days in medicine, that he undoubtedly learned more in one year than the average student could assimilate in three, that he utilized to the limit every educational facility available to him, this training was more than enough. With the possible exception of ophthalmic surgery, in which he later perfected himself under the guidance of his father, Jonas Friedenwald returned to Baltimore in 1923 a remarkably well trained man. He then began practice with his father, and at the same time received an appointment to work in ophthalmic pathology in the Department of Pathology under the late Dr. William George MacCallum. Thus he began his work in the Johns Hopkins Medical School, work which was to continue without interruption until the time of his death thirty-two years later. When the Wilmer Institute was founded in 1925, he was appointed in charge of the pathology laboratory and thereafter was rapidly promoted to instructor, assistant professor, and finally to associate professor. Due to the fixed distribution of academic titles in the Johns Hopkins University School of Medicine, the title of full Professor was denied him. Nevertheless, there never was a member of this faculty who more richly deserved this title. To all intents and purposes in the last fifteen years of his life, Jonas was the revered but uncrowned Professor of Ophthalmic Pathology. He likewise was in charge of and directed the lion's share of the research activities of the Wilmer Institute.

How well he acquitted himself of these tasks is a matter of open record. One has only to browse through the six volumes of his collected reprints to follow the remarkable development of this man. Thus in the early years from 1922 to

1928, we find him exploring little known fields of ophthalmic pathology, often with Dr. Verhoeff or his father as the senior author, but showing the budding of that same insatiable scientific curiosity which was later to blossom into full flower. During this period, while his first interest lay in pathology, one nevertheless finds outcroppings of his fundamental love for physics and mathematics, now perforce directed and crystallized into the field of physiological optics. As early as 1924 he produced a new astigmatic chart, and began to explore the possibility of the use of a yellow-green light in ophthalmoscopy. These early researches finally culminated in the construction of the famous Friedenwald slit-lamp ophthalmoscope in 1932.

In 1929, at the 13th International Congress of Ophthalmology in Amsterdam, Jonas presented the first report of his investigations on the problem of glaucoma. The title of his paper was: "The Pathogenesis of Acute Glaucoma." In this report he clearly established the role of edema of the ciliary body in the pathogenesis of acute glaucoma, and the regular association of ciliary edema, hemorrhagic, serous and fibrinous extravasations with the acute rise in ocular tension. This paper marked a milestone in his scientific career. Not only was it an outstanding and enduring monument to his genius, but it marked his entrance into fundamental, basic, scientific investigation, a delving into the very roots of the genesis of disease which characterized so much of his later work. This was the first of a series of profound scientific papers on the pathogenesis of glaucoma—a continuing study which was soon to make him world-famous.

The story of this great contribution is not easily told in lay language. It began with a study of the mechanics of the circulation of the aqueous—the clear fluid which is constantly secreted in the anterior chamber of the eye and is excreted through a complicated arrangement of channels and veins at the angle of the chamber. From this his investigations proceeded on to the mechanics of the formation of the aqueous, to the permeability of the ciliary body, to the dynamic factors which influenced the secretion both of fluids and of colloids, to a study of enzymatic oxidations and the role of various factors, ascorbic acid, adrenalin, cytochrome C, choline esterase, etc., all of which mediate the passage of fluid across the ciliary-aqueous barrier. This was followed by a study of the mechanism of Schlemm's canal and the factors which controlled and influenced reabsorption of the fluid. These various studies were assembled and formed the subject of his famous Proctor Award Lecture in 1949. His interest in the pathogenesis of chronic glaucoma did not cease with the reception of this high honor. He was still actively engaged in the further investigation of this same problem at the time of his untimely death. Jonas would be the first to admit that this complex problem, the pathogenesis of a disease which causes a high percentage of the world's blindness, is not yet solved. But through his efforts we have come a long way towards this goal. The scientific world

today is indebted to him for the fundamental knowledge on the formation and reabsorption of the ocular fluids which was revealed by his investigations. Without this basic information an ultimate solution of the problem would be impossible. When the pathogenesis of chronic glaucoma is finally resolved and understood, I am confident that the solution will rest largely on the foundations laid down by Jonas Friedenwald.

During the quarter century between 1930 and 1955, Jonas' attention was turned to many problems in ophthalmology other than that of glaucoma. Early in 1943 he became interested in wound healing. In this study he developed a technique which involved a study of the mitotic activity, or cell division and regeneration, of the corneal epithelium. During the war years almost all of the research facilities of the Wilmer Institute were devoted to the study of war gases. One of the most important effects of the war gases of that time was on the eye. By measuring the amount of damage done to the eyes of experimental animals, the military value of various gases could be accurately assessed, and the proper concentration of the gas for offensive use determined. Dr. Friedenwald was in entire charge of this investigation. Some of the reports on this work are still classed as restricted and have not been published. At the end of the war, however, seventeen of these studies were cleared and were published in one volume. Fortunately, war gases were never used, but nevertheless these studies by Dr. Friedenwald and his associates yielded much basic information on the metabolism of the cornea and formed the basis for his further studies on wound-healing.

In addition to these investigations on the pathogenesis of glaucoma, the studies on war gases and wound-healing, there was a steady flow of papers on various phases of ophthalmic pathology. These were not what are commonly called "pot-boilers", but each was either a major or a minor original contribution to our knowledge. These and his other studies culminated in the new "Atlas of Ophthalmic Pathology" recently published by the American Academy of Ophthalmology and Otolaryngology and the Armed Forces Institute of Pathology. His continuing interest in mathematics and physics was constantly reflected not only in his scientific investigations, but in practical, day-by-day work. For example, he served as Chairman of the Committee on Tonometry. Thus he was responsible for the present standardization of tonometers and for many refinements and advances in their practical use.

During the last ten years of his life his investigations led him more and more into organic, enzyme and histochemistry. Jonas was always intensely interested in chemistry and had an amazing knowledge of the subject. When his investigations led him into highly specialized fields, Jonas proved he was no man to follow. He was the one who must lead. He therefore plunged headlong into the study of these highly technical phases of chemistry and in a short time he had reached such distinction that one distinguished professor in this school said:

"This is a most phenomenal spectacle—an ophthalmologist is our foremost authority and most distinguished scholar in the field of histochemistry."

Such was the versatility of this many-faceted genius. And it must be remembered that through these thirty-two years of scientific work, Jonas Friedenwald constantly maintained an office and devoted himself tirelessly to a large practice. He was never too busy or too tired to give his skill, his attention and his time to any needy or ill patient who might seek his help and advice. He guarded his time, because it was imperative that he do so if he was to accomplish the work he laid out for himself. He would not allow the demands of practice to interfere with his scientific or research activities. Large fees and monetary gain could not tempt him to forsake his laboratory or cut short one hour that portion of the time he had allocated for investigation. But he did allow the demands of practice, the needs of his patients and their calls for assistance to cut deeply into the few hours he allowed himself for rest and recreation. And in addition to all these professional activities, as Judge Frankfurter and Dr. Wolman will tell you, he found time to interest himself in art, music, and other cultures and above all, to work intensively for the betterment and advancement of his own people.

When we look at Jonas Friedenwald from the viewpoint of a scientist, what shall we call him—ophthalmologist, pathologist, physiologist, physicist, or chemist? He was all of these, and in certain phases of each field he was preeminent. But he was more than all of these. In addition, he was an inspiration to his colleagues and an unforgettable influence on his pupils, the young men who came from far and wide to work under his direction. He always had the time and the patience to listen to the ideas, the troubles, and the problems of the beginner, to aid him with sympathetic advice, and frequently with practical laboratory assistance. He could correct mistakes and turn the neophyte into the proper paths so skillfully that the straying youngster was often scarcely aware he had wandered away after false gods. Jonas both led the vanguard and encouraged the laggards. I have heard it said that at times he was intolerant of stupidity and obstinacy. If it were so, I never saw it, and in our many years of close association, I have seen him sorely tried. He possessed the sterling qualities of sincerity and tolerance, and these were responsible for the fact that he never excited jealousy or envy in his colleagues when honors were conferred on him. Rather there was rejoicing that a man so loved should receive just recognition. It can truthfully be said that he inspired young men as much by his simplicity, his honesty, and his forbearance as he did by his great scientific achievements.

I cannot conclude without paying to my old friend my own personal tribute. For thirty-two years we were closely associated in the Wilmer Institute. For the first eight of these we worked side-by-side under the professorship of Dr. William H. Wilmer. In 1933 I was appointed the administrative head of the

department, a position for which Jonas Friedenwald was equally well and probably better qualified than I was and which he would have filled with the greatest possible distinction. If my selection was a personal disappointment to Jonas, he never showed it by word or by deed. During the twenty-two years of my administration, up to the time of my retirement and his tragic death, he was not only my loyal friend, but also my faithful advisor, my colleague and my counselor. During this long association my respect and my love for him grew. His personal integrity and sense of honor were beyond all question. I have never known him to countenance a mean or dishonorable act.

In his allegiance to the Institute, no task was too heavy for him, no labor too arduous, if it could be of service to the Hospital or the Department. Often he led, I followed. And so now, when he is gone, I think of him as a great scientist, a true investigator, a splendid teacher, an inspiration to his pupils and his colleagues, and above all, as a dearly loved friend. If I had to express Jonas' many fine qualities and his genius in a few words, I would use Shakespeare's lines:

> "His life was gentle, and the elements
> So mixed in him, that Nature might stand up
> And say to all the world—'This was a man'."

PERSONAL RECOLLECTIONS OF JONAS S. FRIEDENWALD

FELIX FRANKFURTER

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In the privacy of our own feeling we are all heavy-hearted that Jonas was not allowed to run the full course. But that has not brought us together. We are not here as mourners. We are here to convey our gratitude and to reenforce and re-vivify the joy, the stimulus, the strength we can draw from his life and have drawn from it, each in his different way, throughout the years of our relations with him. I am not going to talk on any formal subject because that would not be true to our relations. It is sufficiently significant that one like myself, so far removed from Friedenwald's professional interests, should have been privileged to speak a word on this occasion. I suppose the reason is that someone outside of his more scientific interests ought to give a sense of the amplitude, of the depth and the richness of the man who was never obscured by his profession. As Dr. Maumenee has indicated, I came to know Jonas when he turned up at Harvard, (I was then on its Law Faculty) a youngster having already his medical degree and having already pursued basic mathematical studies at Columbia. In a way that was not the beginning of my relations with him, for I knew, and rather intimately because of our common interest in Zionism, his, what shall I say, that benign gentleman who was his father. Very soon, however, we achieved an independent relationship, for only a most obtuse mind could fail to realize that here was an extraordinary personality.

I happened to have had a good many intimate friends on the Medical Faculty at Harvard, younger men and older men, and it was not at all surprising for one to learn that the great Harvey Cushing detected the qualities of this young ophthalmologist—that is what he was already by a process of osmosis, I suppose, as Dr. Woods indicated, more than anything else—and asked him to make an examination of every patient in Dr. Cushing's ward at the Peter Bent Brigham. Very soon I began to realize that Jonas' interests far exceeded the boundaries, however far-stretched, of the medical sciences. He wanted to know, and this was characteristic of him, about the basic ideas of law and jurisprudence. "What can I read?" We had some talk, a good deal of talk, on and off. He wanted something more than fugitive talk, and so I bethought myself and told him to read Holmes' *Common Law*. That's not an easy book I can assure you, and the lawyers and judges here will bear me out, that Holmes' *Common Law* is indeed tough going. It is not a book for freshmen. And so I gave him Holmes' *Common Law* to read, and he read it. I do not mean he passed the eye over the page. He read it thoughtfully. And I remember well saying at the time to a friend of mine, "This young doctor has asked me more embarrassing questions about some of Holmes' chapters than ever I was asked in discussion

about the book by colleagues of mine on the Harvard Law School Faculty." And that is not a denigrating remark about the members of the Harvard Law School Faculty.

And so the years went on and he came to the fullness of his powers, as Dr. Woods has indicated. Mr. Justice Holmes was wont to say—"I don't know facts; I merely know their significance." I hope I don't appear boastful if I say of Dr. Woods' paper that I could catch some of its significance without even understanding the terms. Jonas and I kept up this intimacy so far as geography permitted. But after all one can write, he did come occasionally to Boston, I did come to see him at Baltimore, and eventually I was transferred to Washington. From my early reading days I gathered something of the great controversy regarding the role of heredity as against environment, what is nature and what is nurture. In the case of Jonas he undoubtedly started with a superlative brain, a superlatively unique equipment that was his, that was nobody else's. As has already been indicated, however, the two powerful forces that brought glory and developed the native, indigenous qualities of Jonas, were of course the great tradition into which he was born and the environment which he found here at The Hopkins. I think Dr. Woods said he absorbed so much at home that in one year he acquired knowledge that it takes even good students three years to make their own. But he absorbed more than knowledge. He absorbed a comprehensive, cultured outlook on life. His father, I need not tell a Baltimore audience, was one of the most cultivated of men. His grandfather was a man of originality, pertinacity and curiosity of mind. And his great-grandfather evidently had those qualities of enterprise and courage which in different aspects and through different modes, Jonas disclosed. He revealed them in the adventures of his mind.

Then there was The Hopkins. Thanks to this occasion, I found it a liberal education to read a sizeable library on The Hopkins. This is to understand the kind of environment into which Jonas came. I do not think it is a language of hyperbole that led Dr. Simon Flexner to speak, in his Life of Dr. Welch, of the heroic age of medicine. All the fortunate, fortuitous circumstances by which some people were called here and by which some people did not come, all the enterprising genius of President Gilman, led this to be the great seed bed of adventuresomeness, of daring, of enterprise, of enthusiasm—that great dynamo of thought—to be the place in which Jonas was nurtured. Here he had as examples men who were not just doctors but in whom doctorship was part of a full life. The great man and enchanting creature that he must have been, Osler, was gone. But when a man like that leaves, something of him, a good deal of him, is left behind. But Popsy Welch was still here, and Halsted was here, and was Dr. Howard Kelly here during Jonas's student days? But, then, he is to me more elusive. I should not suppose that culture was the dominant quality of his life. In their different ways they were all great men. They had zest, zest for

inquiry. They were not confined and imprisoned, as most of us are confined and imprisoned in our respective professions. And that inquiry of Jonas', "I want to know something about the basic ideas governing law, the fruitful theories in the law," persisted in him, not only as to law, but as a good many of you know, in other domains of man's adventures. But law continued to be a rather, what shall I say, considerable side-interest of his. And I began to realize that the old notion of the separateness of the sciences, not only the separateness of the sciences but of interests outside the natural sciences, was fast going. There was a realization in educational institutions and in the minds of men generally that problems which theretofore had been deemed distinct imperceptibly slid one into another. And so the great questions, not only of medicine but of law, became not merely the technical content of this or that course or of this or that problem, but questions that were relevant to problems to which specialists give their lives, but which become clearer by asking profounder questions. The questions that became clearer and profounder were the common questions bearing on the creative process, how do we think, what we think, what are the farther reaches of what we think.

Now law and medicine have some kinship. Law, of course, more or less reflects (usually less than more) the advances of thought in every domain. But in relation to medicine it has, of course, some immediate concerns. The criminal law, not merely the bearing of insanity, but the whole domain of criminology, derives from, or is based on, assumptions which one is again and again convinced are outmoded assumptions of fact. Take the patent law. What is an invention? How do you determine what it is that has been invented? Lawyers talk about laws of nature—a phrase infected by evasions and ambiguities. What are the laws or works of nature? You can see how Jonas, having an intellectual holiday from his profession, and I, eager to get what glimpses I could on intellectual issues that were outside my daily concerns but relevant to them, would have a grand time throwing balls into each others court. And you will readily appreciate what relish and stimulation I derived from such talks. Sometimes things got put on paper. In the realm of ideas there is no hierarchy. There is not an older man and a younger man. Ideas are not ticketed according to protocol. One of the things I got out of my reading about the early Hopkins days—and I hope they still are the same—was that lines were crossed between the old and the young in adventures of the mind. Such it was between Jonas and me from the time he was a lad till the other day. Sometimes it was a specific problem which I would put to him. Sometimes it was a specific problem that he encountered in his reading or reflections which he would put to me.

It always seemed to me that the way to honor a man's memory, whose influence persists, is to convey him in his own person. How did he express himself? What did he think when he put his slippers on, what was he like in his intellectual bathrobe? What did he put on paper when he had little thought

that anybody else except the recipient would read it? And so I went through the file of my correspondence with him over the years. And with your permission I should like to read some of his observations which give point and concreteness to what I'm trying to say about the untrammeled quality of his mind, the realization that courses are devices of educators and do not exist in nature. There are interrelations that disclose ultimate questions of concern to the lawyer, the engineer, the artist, the doctor, even the judge.

From time to time I have been troubled to understand what is really meant by "science", what constitutes "science", in any respectable use of the term. So I asked him once if he would put on paper what to him science is, and I will read his reply. I will read it to you with a great deal of confidence that it is important because a distinguished scientist to whom I passed it on was so struck with it that he asked Jonas if he might quote it in something he was writing. Here it is.

"Science is a social phenomenon. A scientific discovery does not become part of the body of science until it has been comprehended and confirmed by others. Even the most private scientific activity of the individual scientist must be based on the comprehension of what others have contributed. Consequently the language of science is as much a tool of scientific progress as any mechanical gadget which we use. If we allow that tool to be dulled, progress is slowed." Imagine what a fruitful line of thinking and admiration that opens up to the lawyer and the judge whose tools are words and nothing but words. "This presents a continuing problem because the advance of knowledge results in the continuous change in the meaning of words." A whole book on constitutional law could be written with that as the legend on the title page. "When we succeed in inventing scientific words of enduring usefulness, we do so largely by naming the invariants we have discovered. In such case the advance of knowledge sharpens the denotation of our words and enriches their connotations. On the other hand, when we have not discovered the invariants and are forced to give names to evolving forms—such as sovereignty or senescence—" think of combining in one, generalizations, sovereignty and senescence! "Progress of knowledge on social evolution may still enrich their connotations, but, unfortunately often shifts their denotations. If we ignore these shifts, we end up by talking incomprehensively, with rich connotations about an unspecified subject."

I canvassed a problem with him in connection with the conduct of a great educational institution, involving the relation of high scientific endeavor to the conditions under which scientific endeavor can be fruitful. Listen to this. "The talent for deliberative wisdom is most rare, I suppose, no less rare among natural scientists than among others. Perhaps one reason is that it requires some practice to develop, and our living today is so devoid of cooperative effort that we do not learn how to deliberate together. Certainly the whole training of a

natural scientist is pointed in another direction. One of my old teachers used to say that the university was a place where a man with some talent for teaching was forced to do research, and a man with some talent for research was forced to do administrative work. The exceptions are the rare administrative geniuses like Popsy Welch and that wise old recluse, J. J. Abel, one of my high Gods who refuses to allow his administrative responsibilities to grow beyond the scope of easy and intimate management. Yet surely we should learn to manage our affairs more wisely for, otherwise, the ——'s of the world manage them for us.

"What are we to do about these fellows? Down here we have enough of them and I wish I could feel that the medical school does not suffer under their guidance. My own strategy has been to hew out an impregnable fortress for myself and to give advice only when I am asked. While this works fairly well, at least for the individual in the natural sciences, I am not sure that the social sciences can be successfully promoted on such an individualistic basis." (And you will forgive this personal reference, but it is relative to my sketch of him.) "So it seems to me that we need most urgently the stimulus and wisdom that you bring to this problem and it becomes very important that the painful experience with ——— should not discourage him from applying the effort elsewhere. The stakes are too important."

I wrote a friend of both of us of a talk I had with Jonas in which he told me a story that sheds light on his relaxed temper of mind. His motto seemed to have been "ohne Hast, ohne Rast," without haste, without rest. Serenity it is, serenity, which, I think, is hard to attain unless the good Lord deposited something of what we call humor. I had occasion to repeat to Jonas the cynicism of a friend of mine about the medical profession. Jonas said that it reminded him of a minister who came to see him recently who was suffering from eczema. "He had your friend's cynicism about the medical profession and said to me, 'After all these years of medical research I do not see why your profession has not found the cause of eczema.' I offered to bet him ten to one that we would find the cause of eczema before he found why the righteous suffered."

Having read an article by a writer of considerable reputation on a psychological matter that puzzled me, I asked Jonas whether the article was so obscure to me because the writer was too profound for my understanding or whether he was too muddleheaded to be clear. After analyzing some of the illogical positions taken by the writer, and in passing, making some reference to Marx and Freud and how both of them were misled by Hegel, he made this delicious comment: "No doubt economics and psychology are difficult subjects, but I do not think their difficulty is minimized by rejecting criteria for verification."

From time to time he wrote me about Supreme Court opinions and I'll read you his comments on two opinions dealing with very different subjects. One dealt with the problem of disposing of a claim of insanity intervening after a

conviction for murder. The law being settled that society does not hang or electrocute an insane man, the question arose, as so often the question arises, not merely what is abstractly the right answer, but who is to determine it and by what procedure will you get the appropriate light and avoid darkness? The Court had such a case in which the question was whether a governor could decide *Ex parte*, on private advice that a man was not insane without giving the victim, or those near him a chance to be heard. Listen to this for a fellow who was ticketed an ophthalmologist: "I am intrigued by the Solesbee case because of the evidence it seems to me to bear on the decline of Christian doctrine. For those who do not believe in life after death there does not seem to me anything especially inhumane in executing an insane person. The argument that a person who becomes insane while awaiting execution is thereby deprived of the possibility of presenting some extenuating evidence makes sense in relation to due process," (and he was unafraid of these big terms, you know. He knew most of them were stuffed lines.) "but only at such a technical level that a violation of due process in this respect can hardly be called an offense against the basic and popularly held mores of our society. It seems to me, therefore, that the moral revulsion against execution of an insane person in the past must have had its deepest roots in the belief that the unshriven soul is damned. Evidently, thus, this belief is not potent among the brethren nor, in their opinion, among the people of this country at large. I wish that I could feel sure that the decaying Christian morals are being replaced by something as good or better."

Then there was another case in which he thought the court was too lenient. This is undated, but plainly it was written on one of your delightful summer days. "It is hot and sticky down here. I have been trying this Sunday afternoon a combination of beer and electric fans, but I am beginning to think that they cancel each other out. The decision in the revocation of naturalization case is bitter medicine for me to swallow, though being a good patient I earnestly expect that it will do me good. However, to get it down I needed something of a mystic faith in the law analogous to your mystic faith in medicine. What I have trouble in understanding are the criteria by which a court decides between the obvious," (and this is about as, I am sure Judge Niles will agree with me, penetrating a comment on problems of jurisprudence as you can concoct). "What I have trouble in understanding are the criteria by which a court decides between the obvious and simple justice in an individual instance and the principles of supposedly wider applicability. In this instance the choice was no doubt made easier because nobody suffers directly and personally through giving this fellow more than he deserves, but in the long run, are the general principles anything more than an aggregate of individual instances, and what bearing has that aggregate upon the exceptions which fall outside of its domain?"

You will recall that he had read Holmes in his young Harvard days. Some ten years later he returned to Holmes. What he wrote me led me to suggest

that he misapprehended Holmes. This was his reply: "I see now that Holmes's contribution is much greater and more profound than I had thought, and that he has not merely followed the historical path of the evolution of the law, but has also sought and found some of those far, bright, abstract principles which have determined the evolution. This is so far beyond anything that I had realized that I now very much want to reread the *Common Law*. Can you suggest any elementary book which I might study first in order to familiarize myself with the meaning of the technical legal phrases which helped to obscure my understanding at the first reading?" Is it any wonder that this is the fellow who took along for his vacation reading Gibbon's "Decline and Fall" and read all the six portly volumes, and who was one of the very few people, at least in my acquaintance, who actually read all of Toynbee and not merely ah'd and oh'd about it, or damned it at second-hand or on the basis of tid-bits.

Now these are from his letters. I should like to read you two extracts from letters I wrote to him which happened to have been dictated. I read them because they illustrate his impact on at least one man whose life is spent in totally different vineyards of learning and inquiry. He sent me a rather long letter that he wrote to the Baltimore Sun. He called it his first polemic effort. He was aroused by what he deemed less than adequate treatment by the Baltimore Sun of matters concerned with social-economic legislation. In his covering note to me he said, "I hope you do not think too ill of this. It is my first effort at polemics." In part, I wrote him: "I take comfort in the thought that you are habituated in your primary devotion to ophthalmology and that, besides, you have an iron, even if genial, will. That your excellency as a painter has not diverted you from your primary allegiance to science gives me assurance that your new found talent as a political controversialist will not divert you from your laboratory into the arena. If your correspondence with ——— be the fruit of your first political polemic, anybody else but you would be tempted to abandon science, painting and law and all your other prior pursuits in order to become a modern Bagehot. You illustrate once more that good writing certainly as a foundation means having something to write about, and you certainly seem to have mastered the particular items on which you had a real case against the Sun."

And now let me read you the last letter that I had occasion to write him, not knowing it was to be the last. I had sent him a paper I had then recently delivered on which, believe me I'm not boasting, I had spent months of worry, reading, thought and writing. And in that paper of some twenty-five pages he picked out for special mention the one sentence that I would on the whole have least liked to spare. And so I wrote him: "By pouncing on the particular sentence that hit you in my Harvard Marshall Address, you remind me of your perceptiveness more than thirty years ago in matters legal. In response to your request for something that would shed light on basic legal concepts, I suggested

Holmes' *Common Law*, not at all an easy book. You put some questions to me, after your reading of it, which led me to say that your inquiries were more searching than I had experienced from most of my colleagues on the Harvard Law School Faculty!" I read all this for my last sentence. "You give proof to the truth that even the most seemingly disparate problems of the mind are not without some affinities—certainly affinities in the ways of getting understanding of them."

I said we are not here as mourners. How could we be in light of that previous quotation which three colleagues of his have given us in their memorial notice of him, his profoundly moving and intrepid words when the ominous diagnosis was made in August, expressing his "firm determination to squeeze as much joy and interest, love and meaning out of the time still available as possible." Viewed in these terms the extent of that time is a blessing for all of us. And so I say:

> Nothing is here for tears, nothing to wail
> Or knock the breast; no weakness, no contempt,
> Dispraise or blame; nothing but well and fair,
> And what may quiet in a death so noble.

JONAS S. FRIEDENWALD—HIS CONTRIBUTION TO MEDICAL EDUCATION IN ISRAEL

ABEL WOLMAN

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Joseph Stein Friedenwald, a most distinguished son of a distinguished father, was almost inevitably conditioned for the role which he played in society, by his forebears and by his environment. Coming from a family of physicians of wide renown, his interest and accomplishments in medicine might have been predicted. That he would be more than a useful member of society was equally predictable from the attitudes toward and the concerns with the ills of people daily displayed in his immediate household. His grandfather, his father and his several uncles were actively engaged in the fields of medicine, where kindness, mercy and compassion through the ages have been major characteristics and motivations. It is of more than passing interest that, in one of the documents of his father, the reproof which Ezekiel hurls against the rulers of Israel, was approvingly quoted, in the following terms: "The weak have ye not strengthened, neither have ye healed that which was sick, neither have ye bound that which was broken." But the man whom we honor today did pursue a lifetime of sympathy with people, following the dramatic injunction of Ezekiel so frequently emphasized by his father.

Others have already spoken of the contributions of Jonas Friedenwald to the American scene. The area which I shall review represents an extension, both geographically and emotionally, of his interests and devotion. The simple rehearsal of his activities abroad and particularly in Israel do not in themselves give the complete picture of the man. They are essential, however, to illustrate the scope of his interests, the intensity of his purpose and, fortunately, the fruition of his designs.

The concept of the establishment of a medical school in the Middle Eastern country dates back slightly over a quarter of a century, with the endowment of an Institute of Microbiology at the Hebrew University. Only a few years later the idea of a post-graduate school of medicine came under discussion. From that time to the day of his death Dr. Friedenwald was one of the prime movers in the development and ultimate implementation of this idea.

In that interval of some 25 years, he was, at one time or another, a member of the Board of Governors of the Hebrew University; of the Medical Reference Board, which had much to do in developing the salient features of a medical school; of the Development Committee itself; the Chairman of the Subcommittee on Medical Education and of the Curriculum Committee; and in more recent years, a member of the Medical Advisory Board of the Hebrew University.

Throughout this period, aside from advising on general fellowship problems, he made specific contributions in arranging programs for distinguished workers from the Middle East to pursue their advanced studies in the United States. During this period some 90 Fellows from Israel were trained in this country in the medical, public health, medical and hospital administration and paramedical fields. As a matter of fact, the larger part of the medical school faculty in Israel is composed of Fellows who have been trained under this program. To them Friedenwald was mentor, guide and father confessor.

The range of his interest in these enterprises was amazingly wide. His contributions to the evolution of medical education in the Middle East were equally surprisingly great, when it is remembered that simultaneously he was pursuing a career of medical practice, research and teaching. Any one of these duties would have burdened the average individual to the point of mental or physical collapse.

During World War II, when many foreign countries were plagued by the difficulty of obtaining essential pharmaceuticals, he was instrumental in developing in Israel the production of these drugs, and more important, in stimulating the creation of a Division of Pharmacology, which would press forward original investigation in this important field.

In this enterprise he exhibited his extraordinary skill in translating technical concepts and phrases into the simplest and convincing ideas for lay understanding and acceptance. For it was from intelligent laymen that he drew forth his greatest continuing support. He spoke before the Annual Convention of Hadassah[1] in 1942 on that unromantic topic of the difference between pharmaceutics and pharmacology. He succeeded as always in having his way and more important in getting the money to plant the seed for the ultimate creation of a Pharmacology Institute, via the interim limited project of a Pharmacology Section attached to the Department of Pathological Physiology of the Hebrew University.

In this speech he ruefully pointed out the dilemma with which he was always confronted. "You see," he said, "while we of the Medical Reference Board have been educating Hadassah to speak in long poly-syllabic technical words, they are forcing us to learn to speak in words of one syllable. For a medical man who dearly loves his medical vocabulary, this is no easy task!"

During the period in which the Medical Reference Board acted, as he described it, as the obstetrician at the birth of a medical school, he devoted what ordinarily might be considered almost full time to the details of this project. In that process he was at particular pains to emphasize the significance of having a medical school which would be of the breadth and depth which a growing country must have for its spiritual and physical well-being. It is on this basis

[1] The Women's Zionist Organization of America.

that he extended his emphasis and concern to include a school of dentistry as an integral part of the entire medical enterprise.

How well did these ideas fare? Dr. Friedenwald lived long enough to see, as is rarely given to most people, the blooming of many of the proposals in which he so successfully participated. In May 1949, the Medical School was opened and since 1952–1953, a full 6-year course has been offered.

In November 1953, the School of Dentistry and the School of Pharmacy were opened under the auspices of the Medical School. To many of us the dental curriculum is of significance, since it will comprise six years of studies, in the pre-medical, pre-clinical and clinical fields, all closely associated with and part of the medical school itself.

The number of students enrolled since 1951 has been around 400, with the promise of a long and successful accomplishment in education, training and research, already participated in by Christian, Jew and Moslem.

The bare enumeration of some of the factual aspects of his interest illustrate perhaps too well the comment of Macaulay over a hundred years ago that "facts are mere dross of history." What of the man back of these facts? What kind of a person do we speak of when we rehearse the list of these interests and accomplishments? He is, of course, revealed by these accomplishments, but more significantly by the fashion in which he molded them.

Under a sobriety of countenance, which was in fact only monomolecular thin, a sense of humor, a humanity and even an anger could be and were manifested on appropriate occasions. In his pursuit of the objectives listed he encountered of course all of the human obstacles so familiar to most of us who deal with institutional matters. His comment, for example, in one of his reports merely demonstrated the universality of the problems and of the people with which he dealt. He speaks of the situation in Israel in the following terms, and one can detect numerous American analogies: "the rigidities and legalities of the university structure are such that the majority see only those organs of the university which are immediately adjacent to them in the structural hierarchy, and tend to blame these adjacent organs for the difficulties which they encounter." Only a dean and a president can appreciate fully the thoroughness and the significance of the diagnosis.

The university administrator may be further heartened by the additional observation in his report: "Consequently the office is continuously bombarded by requests from the faculty which, in aggregate are wholly incompatible with the budgetary capacities, and which are in each case supported by the maximum available academic authority. It is no wonder that they have adopted the general principle: when in doubt say 'no'."

A sympathetic note in this audience will meet his further concern that "the problem of full-time or part-time or modified part-time has not been settled. . . .

No difficulties are anticipated outside of the surgical specialties." He, too, was a prophet in the land which gave the world so many prophets.

The road to accomplishment was never too easy. The devices which he used to stimulate, to cajole, to fight were interesting to observe, but the persistence in attaining the goal was never flagging, except once. I recall a session of the Medical Reference Board with representatives from Israel, at which the transactions had lasted during a very long day. The subtleties of university-medical school relationships were pursued in tireless and ultimately tiresome detail. Their contradictions and contests had reached a maximum level of human endurance. With the same mildness of attitude he had so often displayed with his patients, but with a flashing eye, he announced that if the one group persisted in its present stubborn intentions he would resign. This startling and unexpected threat on the part of an individual whose voice rarely rose above the conversational acted as a coagulating agent and precipitated most of the differences of opinion, leaving a clear agreement. To this observer, it was a pleasure to see this demonstration of anger, so rare and yet so necessary an attribute of a human being. It was successful, because it was known to be so rare.

His sense of humor, always gentle and rarely biting, was more often apparent. His appearance before one thousand ladies to discuss pharmacology is a case in point. He ended his clear exposition of the subject by begging to be excused from the platform on the score that women in large numbers intimidated him more than the subject did.

As he conceived of the Medical School in Jerusalem it was a natural reincarnation of an institution to perpetuate the spirit of Maimonides, of Henle, Cohnheim and Weigert in pathology; of Senator, Hayem and Boas in internal medicine; of Romberg and Moll in Neurology; of Caspar and Lombroso in forensic medicine; of Metchnikoff, Frankel, Haffkine, Neisser, Wassermann and Ehrlich in the science of infection. It was as if he visualized that, out of the flames of Hitler's crematoria, a new university–medical institutional Phoenix would rise, literally fertilized and enriched by the tragedies and offspring of the devastating past. Here in this soil of the East, after a thousand years or more, medical science and education would return for a new flowering.

This development was not to be a mere image of western medical education and research. The problem of fusing a faculty with many lands of origin and many different backgrounds of training was both a challenge and an "enormous potential advantage." He pointed out that often the great schools of the past were developed out of emigrés and through the fusion of different backgrounds, brought about something new and unique.

He was aware that such a school had to be unique, because already medical practice in Israel was perhaps further on the road toward socialization than anywhere else, perhaps with the exception of Russia and the Scandinavian

countries. A special burden was placed on the medical school to train doctors as servants of the community, more so than as private practitioners.

Hence, he felt that the problems of public health and preventive medicine, as parts of the medical curriculum, were of more immediate acuteness than in some other countries. He predicted that these influences would deeply color the medical school's development.

How close to our home environment he touched as far back as ten years ago, when he reflected on how to teach preventive medicine and the social aspects of medicine to the medical student in the Middle East. He said then: "It involves an institutional problem which has not been solved satisfactorily anywhere in the world, because medical schools are built around hospitals. In a hospital, the student has the opportunity of learning to diagnose and cure sick people, but he has no exposure to the problem of preventive medicine in any sense."

"Unless hospitals are expanded to take in the preventive medical field, some other institutional framework will have to be linked to the medical school in order to form a public health laboratory." He thought that in Israel such institutional resources were available and could be easily and strongly linked to medical school and hospital purposes and functions. Here was a unique laboratory for instruction in preventive medicine, where medical school, demonstration public health centers, university and health department were already closely linked in origin, in spirit and partly in management. A real charter for the future! Its assessment only time will disclose.

He made several visits to Israel, one in 1936 and the other in 1945. During the first period he was a visiting lecturer at the Hebrew University. In that undertaking he demonstrated once again the thoroughness of his approach to any challenge. He delivered his lectures in Hebrew, in which language he had been tutored in this country for many months before entering his assignment. His competence in the official and hereditary language of the country is attested by the story, which I assume is not apocryphal. His wife accompanied him on this trip and attended his lectures. During one of them a man sitting next to her said, "I don't know about the ophthalmology, but the Hebrew is excellent." Mrs. Friedenwald, well endowed in her own right, responded, "I don't know about the Hebrew, but the ophthalmology is excellent."

Unexpected softness and tenderness in attitude frequently came to the surface with those of us who had the pleasure of knowing him more intimately. These characteristics gave the wider basis for his extreme interest in the individual and in society as a whole. Dr. George Corner and I, attending a meeting of the National Research Council in Washington a few years ago, had agreed to wait for Dr. Friedenwald who was at another meeting. He was to drive us to Baltimore. Through circumstances which were undoubtedly legitimate, he was some two hours late in picking us up. In the meantime, a distinguished Balti-

more artist, Eddie Rosenfeld, had arrived at the Cosmos Club to join us, also for transportation to Baltimore. When Dr. Friedenwald finally arrived to pick us up, the three of us plagued him in our own persistent ways on the return to Baltimore. His explanations and apologies were extensive, clear and, of course, convincing.

The following day Mr. Rosenfeld appeared at Dr. Corner's and my house with a lovely drawing in color for each of us as a testimonial from Dr. Friedenwald of his apologies and delinquencies, a permanent reminder of the extraordinary human instincts which motivated him.

As I speak, I have the uncomfortable feeling that Dr. Friedenwald is at my shoulder looking somewhat reprovingly at me. I know he would force me to say that I have attributed to him ideas, accomplishments and inspirations to the development of medical education in the Middle East, which are by-products of more than a single individual. He would insist that I state that on the Medical Reference Board a number of distinguished Hopkins graduates gave time, energy and thought to the same enterprise. He would undoubtedly emphasize the contributions of Abraham Flexner, of the late William A. Perlzweig, of Harry Eagle. But I am equally positive that I could make a good case with him, in which all of these gentlemen would have whole-heartedly agreed that to Dr. Friedenwald belongs the major credit for the long sustained and successful conversion of an idea into an accomplishment of major permanent significance to the entire near and middle East.

The first Chairman of the Medical Reference Board, Dr. Bluestone, makes the important observation that: "If Jonas Friedenwald were a little more outspoken and a little less self-effacing, there would be a permanent memorial to him in the medical school which now exists largely through his continuous efforts."

Within the past 30 days the National Board of Hadassah has voted to name the Retinoscopy Room of the Hadassah Hebrew University Medical Center in memory of Dr. Jonas Friedenwald, as an indication of their tremendous debt to him.

In his earliest survey of the necessity of a great medical center in the Middle East, Dr. Friedenwald pointed out the absence of large centers of medical education in this vast area. It was his matured view, recently so well phrased by George Wilson Pierson of Yale that "nations without universities are treeless plains. . . . Universities without colleges are hollow trees." As he pursued these tasks he never lost sight of their central objective, namely, to lessen the burden of man, in which task skilled and thoughtful streams of young men supply the major lifeblood. Throughout his career he followed Abraham Flexner's dictum in designing the elements and the structure of the school. When Flexner was asked what should be included in a medical school, he responded succinctly: "Get brains and put them to work."

In closing this much too feeble and limited picture of this man in society, I feel almost apologetic in having spoken about Dr. Friedenwald in the past tense. This is essentially an inaccuracy, for his spirit, his works and his personality are here today and for innumerable tomorrows hereafter.

ABSTRACTS OF PAPERS PRESENTED BEFORE THE MEETING OF THE JOHNS HOPKINS MEDICAL SOCIETY

April 9, 1956

THE FUNCTIONAL ORGANIZATION OF A CEREBRAL CORTICAL AREA

VERNON B. MOUNTCASTLE

A short summary of the present knowledge of the location and extent of the areas of the cerebral cortex which receive impulses ascending the great afferent system of the brain was presented. Reasons were given for turning from studies of the geography of the cerebral cortex to the problem of how cerebral cortical areas are functionally organized. The method of single unit analysis has been applied to this problem, specifically in an attempt to determine the way in which the neurons of the somatic sensory cortex of the cat (post-central homologue) respond when brief stimuli are delivered to sensory receptors of the skin, or of deeper structures of the body.

The conducted impulses of single cortical neurons have been recorded via extracellularly placed 3–4μ microelectrodes. The electrodes were carried in a microdrive mounted in the sliding outer wall of a fluid-filled chamber, sealed to the skull over the opening in bone and dura. This allowed variable positioning of the electrode, and its insertion in 5μ steps. The hydraulic fixation prevented cortical movements without pressure injury; insertion injury was greatly reduced by micro-dissection of pia-arachnoid from the chosen site of entry. In this way the activity of single neurons can be observed for several hours, if desired. Experiments were performed on cats under light barbiturate anesthesia.

Those cortical neurons driven by transient cutaneous stimuli respond with a short train of conducted impulses. The latency, frequency and modal value of this repetitive train are exceedingly stable when the stimulus parameters are constant, and are sensitive indices of the intensity and frequency of the stimulus; they vary also with change in the position of the stimulated point within the peripheral receptive field of the neuron.

Three lines of evidence have been obtained which support the hypothesis that, for the early repetitive response, the sensory cortex is organized in vertical modules of groups of neurons, these modules forming an interlocking mosaic. These lines of evidence are:

1. When an electrode enters the cortex perpendicularly to its surface, all active neurons encountered through the depth of the cortex are related to approximately the same peripheral receptive field. Measurements of the areas of these fields indicate an inverse relation of area to peripheral innervation density.

2. Neurons representing three sub-modalities have been encountered: those responding to movements of hairs, others to pressure upon the skin, and still others to movements of joints or stimulation of deep fascia. No cross activation between these submodalities has been observed. If an electrode enters the cortex perpendicularly all active neurons encountered in the penetration are related to one and the same submodality (85 per cent of all penetrations). A startling observation has been that cortical neurons reflect the discharge properties of the peripheral receptors to which they are related, e.g., in the property of rate of adaptation, a fact reported several years ago by Adrian. Neurons related to joints and joint capsules are sensitive indicators of steady limb position and of rate of change of that position.

3. Neurons in such a vertical elementary unit, all activated by the same mode of stimulation from the same receptive field, respond after almost identical latencies (within 1.0 to 2.0 msec.), regardless of the cortical layers they occupy.

This hypothesis of functional organization relates only to firing patterns formed during

the early repetitive response of cortical cells. Activity occurring later in time may form sequential firing patterns of quite different nature.

UROPEPSIN AND PLASMA PEPSINOGEN

ALBERT I. MENDELOFF

A brief review is given of the history of assay of proteolytic activity of urine at acid pH. Present controversies about the relationship of urinary pepsin activity to gastric pepsin secretion are discussed. Evidence is presented which casts doubt that the uropepsin excretory rate is constant in diurnal and nocturnal urines, and the use of a creatinine—uropepsin ratio instead of total urine collection is shown to be an unreliable method of estimating uropeptic output.

By comparing the concentration of pepsinogen in plasma from the left gastric artery, the gastroepiploic vein, and the portal vein, the gastric blood supply in anesthetized human subjects is shown to account for from 10–35 per cent of the total portal inflow.

In acutely bleeding or very ill patients with duodenal ulcers, a large number of urine samples were found to have no demonstrable peptic activity for several days after hospital admission. It is suggested that pepsin inhibitors may account for these findings.

Certain conclusions are made as to the general validity of present concepts of pepsin and pepsinogen secretion.

STUDIES ON THE MECHANISM OF INJURIOUS ACTION OF BACTERIAL PYROGENS

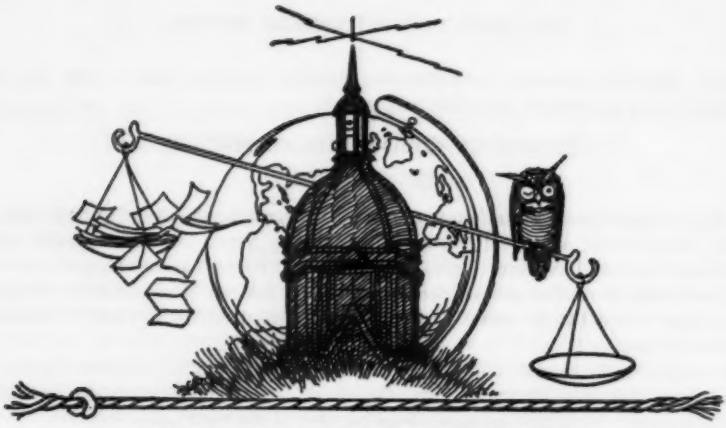
LEIGHTON E. CLUFF*

Bacterial pyrogens or endotoxins associated with gram negative bacteria may produce fever by direct action on the central nervous system, production of tissue injury resulting in formation of an "endogenous pyrogen", or interaction with a component of blood forming a pyrogenic material. Bacterial endotoxins brought into contact with normal serum, plasma or blood prior to injection into man or experimental rabbits are augmented in their injurious action. The effect of serum on other biological properties of an endotoxin from *Shigella flexneri* was studied, and found to alter its antigenic and immunological activity when analyzed by precipitation in gel. Electrophoretic fractionation of serum, with analysis of individual protein components for their effect on the immunological reaction of the toxin showed that beta globulin contains the component probably responsible for this effect of normal serum. A similar effect of serum on the immunological reaction of non-pyrogenic polysaccharide and protein antigens was not observed.

Repeated injection of pyrogen into man or experimental animals produces a state of tolerance to the pyrogenic effects of the toxin which is nonspecific and unrelated to the usual mechanisms of antibody. Serum from tolerant animals is less able than normal serum to augment the injurious action of endotoxin. In addition, tolerant animals' serum was found to alter the immunological reaction of pyrogen, but to a less degree, quantitatively, than does normal serum.

The possible role of a serum component in the biological action of endotoxin or bacterial pyrogen is indicated, and suggests that changes in this host factor may participate in development of "tolerance" or increased susceptibility to the toxin observed under certain conditions, i.e. shock, etc.

*Cluff, L. E.: J. Exp. Med., 1956, **103**: 439.



BOOK REVIEWS

(These reviews represent the individual opinions of the reviewers and not necessarily those of members of the Editorial Board of this Bulletin)

Principles of Renal Physiology. By HOMER W. SMITH. 237 pp., $5.00. Oxford University Press, New York, N. Y.

This book is obviously a condensation of the author's "The Kidney: Structure and Function in Health and Disease," and appears to be written for students and other beginners wishing to obtain an introduction to the present status of renal physiology. The usual preface is replaced with a dozen stanzas of Lucretius' *De Rerum Natura*. There are nineteen sections or chapters with six appendices. The first seven sections on anatomy, historical note on theories of renal secretion, rate of glomerular filtration, tubular reabsorption and tubular excretion present in a clear and concise manner the present status of renal function. The later sections amplify the central concept; they discuss such topics as fluid compartments of the body; water diuresis and antidiuresis; excretion of urea, proteins, strong electrolytes, acid-base, ammonia synthesis and excretion; and control of the renal circulation. The appendices deal with such topics as electron microscopy of the nephron, calculation of body surface area for dogs and men, methods of measurement of renal clearances with detailed analytical methods, etc.

The treatment is somewhat rigid and dogmatic, but one gathers that the author is quite aware of this. Problems for solution are presented in various parts of the text, and should prove valuable for those students who desire mathematical representation of a concept. A certain amount of the text is in fine print and could be omitted by the beginner. The appendices do not seem to this reviewer to be valuable for the beginner; but since they are in fine print, they could be omitted. The bibliography is extremely well selected and should prove of great assistance to the student wishing to pursue the subject further.

This book can be strongly recommended as an excellent introduction to renal physiology.

E. K. MARSHALL, JR.

Obstetric Practice. By HAROLD SPEERT AND ALAN F. GUTTMACHER. 478 pp., $7.00. Handbooks for the General Practitioner, Landsberger Medical Books, Inc., distributed solely by The Blakiston Division of The McGraw-Hill Book Co., New York, N. Y.

This handbook, in its 450 pages, presents a wealth of information for the general practitioner. The book is instructive, well organized and easy to read. Like all handbooks, how-

ever, it suffers from being overly concise. Little or no choice is given to the reader as to various procedures or methods of therapy. A specific drug is recommended, usually by its trade name, with no or at most one alternative. Some readers will take exception to such dogmatic statements as "Hormones are of no value in salvaging a pregnancy that is threatening to abort." The description of certain difficult and dangerous operative procedures (such as Dührssen's incisions) are apparently included in the text only for the sake of completeness and are not recommended to the general practitioner. The absence of illustrations, charts and bibliography lessens the attractiveness of the work. The chapters on Toxemia of Pregnancy and Obstetrical Analgesia and Anesthesia are particularly worthwhile. The general practitioner who seeks help on even the most complex obstetrical problems will find such help clearly and simply expressed. The handbook should prove of value to its intended audience.

JOHN M. SPENCE, JR.

The Interpretation of the Unipolar Electrocardiogram. By GORDON B. MYERS. 164 pp., $4.75. The C. V. Mosby Co., St. Louis, Missouri.

Clinical Electrocardiography. I. Arrhythmias. With an Atlas of Electrocardiograms. By LOUIS N. KATZ AND ALFRED PICK. 737 pp., $17.50. Lea & Febiger, Philadelphia, Pa.

The first months of 1956 saw the publication of the two new books on electrocardiography listed above. Some general comments are first in order. It is a truism in the medical book trade that "any old" book on electrocardiography sells "like hot cakes". Most of the medical book publishers have at least one in their line and enjoy pleasant profit therefrom. In general, heart disease is considered such a "hot subject" these days on both the clinical and investigative levels that any book on cardiovascular matters has a sizable captive audience which is afraid not to buy the book. One does wonder about the salability of a treatise on merely a segment of the total field of electrocardiography when the book costs $17!

The second general comment concerns the field of electrocardiography. Sir Thomas Lewis abandoned the field over 30 years ago because, in his estimation, the cream had been skimmed off and opportunity for further significant contributions was limited. Although Lewis' judgment was doubtlessly premature, it is in general sound, particularly when translated into the situation in 1956. An acute observer of the contemporary scene in cardiovascular research makes the statement that preoccupation with electrocardiography has set back by 50 years progress on the truly important problems, hypertension and arteriosclerosis. Although obviously hyperbole, here too is a large kernel of truth.

The two volumes reviewed are satisfactory productions; it is questionable, however, that they contribute anything to the previously available publications.

In *Arrhythmias* Katz and Pick also discuss conduction defects. The term "dysrhythmia" has much to recommend its use in lieu of "arrhythmia" but convention probably justifies continued use of the latter term. There are many moot problems about the mechanism of many of the dysrhythmias and many serious workers in this field would not agree with the position taken by the authors. However, it is not clear to the reviewer what practical value these fine distinctions may have.

In *Unipolar Electrocardiography* Myers presents the canonical views of the disciples of Frank Wilson. Here too many serious students would question even basic premises expressed herein. A trend away from the unipolar lead, at least renewed awareness of the duplication of information in the conventional bipolar leads and the unipolar leads, was evident in the recent conference sponsored jointly by the New York Academy of Medicine and the National Heart Institute.

The reviewer cannot wax enthusiastic about either of these books.

VICTOR A. MCKUSICK

Current Therapy 1956. Edited by HOWARD F. CONN. 632 pp., $11.00. W. B. Saunders Co., Philadelphia, Pa.

This book is now in its eighth edition. Each year it is a popular volume, and it is easy to see why this is so. Physicians are repeatedly faced with the need to prescribe, in very specific terms, for patients with given diseases. In these situations, especially if the disease is not common, the doctor is grateful for simple, reliable advice. The fact is, of course, that rational therapeutic regimens of proven worth are not always available. There is nevertheless considerable pressure to do *something* for one's patients, and in the absence of unequivocal data the physician often consults another physician who has had extensive experience in a given field. "Current Therapy" is really a compilation of such consultations. A large number of physicians, famous and not-so-famous, describe briefly their pet therapeutic schemes, going into considerable detail in regard to specific drugs, doses, etc. There is usually no attempt to justify recommendations, since the basic idea of the book is to give concise (and presumably authoritative) directions. In every sense, then, this is a therapeutic "cookbook." There is inevitably a certain amount of art and compromise that is not, or cannot be easily put down in such form.

There is undeniably a place in medicine for a book of this sort, and the choice of many good clinicians by the editors provides for "consultations" that should prove valuable to a large segment of the medical profession. Everyone will be able to find occasional advice in this book that seems poor, but on the whole the brief writeups contributed by the long list of co-authors seem fairly satisfactory. One worrisome thought, however, is that such a text tends to encourage reliance on *ex cathedra* statements unsupported by evidence. It is important to remember that "authorities" not infrequently turn out to be wrong. One major safeguard against uncritical adherence to erroneous dicta is to demand correlation between therapeutic recommendations and successful clinical results, as already mentioned. A second is to perform clinical experiments so as to allow therapeutic decisions to be based on sound data.

LOUIS LASAGNA

Androgens: Biochemistry, Physiology, and Clinical Significance. By RALPH I. DORFMAN AND REGINALD A. SHIPLEY. 390 pp., $13.50. John Wiley & Sons, Inc., New York, N. Y.

The field of endocrinology has become so vast in recent years that special monographs have become necessary to cover comprehensively various facets of the subject. In *Androgens: Biochemistry, Physiology and Clinical Significance*, Ralph I. Dorfman, one of this country's foremost steroid chemists, and Reginald I. Shipley, an experienced clinical endocrinologist, have collaborated in compiling, summarizing and evaluating the available literature on the subject. This will be a valuable and much needed reference volume for the student and investigator in endocrinology. The compounds which are considered to be "androgens" differ, according to whether the term is applied in its biologic meaning to stimulants of male secondary sex characteristics and protein anabolism, or is defined chemically according to the molecular structure. For the most part the authors follow the latter definition and present the information available concerning most of the known *19-carbon steroids* although there are references to "androgenic" properties of some of the 21-carbon pregnene compounds.

The volume may be considered as consisting of two parts of approximately equal length. The first part deals with the biochemistry and physiology of these steroids and the second part with the clinical disorders of androgen secretion and the therapeutic uses of androgen. The section on biochemistry discusses the structure and properties of the numerous 19-carbon steroids isolated from testicular and adrenal tissue, urine and bile, and the nature of the artefacts produced in chemical manipulations. The *in vivo* pathways of synthesis and

degradation are considered in detail. Of particular importance are the derivation of androgens from pregnene precursors and the conversion of adrenal corticosteroids to 19-carbon steroids. Apparently, the recent discovery of the conversion of androgen to estrogen had not yet been announced when the book went to press. In the section on physiology, the effects of androgens on various endocrine glands and other organs and their influence on protein, creatine and carbohydrate metabolism and on numerous enzyme systems are discussed.

The clinical portion of the book deals with the disorders which cause excessive or deficient secretion of androgen. Although the innumerable conditions for which androgen therapy has been advocated are mentioned, the authors fortunately have preserved a reasonably conservative attitude toward its use. The volume concludes with an appendix of 115 pages. This contains the structural formulae of 225 steroids, of which 132 are 19-carbon steroids. There are, in addition, details of the laboratory methods for the extraction, fractionation and chemical measurement of the 19-carbon steroids and for the bioassay of androgens which will be most useful for those engaged in these studies.

LAWSON WILKINS

Hypnotic Suggestion. Its Role in Psychoneurotic and Psychosomatic Disorders. By S. J. VAN PELT. 95 pp., $2.75. Philosophical Library, New York, N. Y.

This book is by a Harley Street (London) therapist, President of the British Society of Medical Hypnotists and Editor of the British Journal of Medical Hypnotism. It is a small readable treatise on the subject, written very much in the style of an article that might appear in "Life" or "Look". Various aspects of the subject are covered: history, theory, technique and case reports. The twelve patients described varied from neurasthenia, insomnia, to migraine, frigidity, asthma and reactive depression: the representative statements of the patients were "enjoys life once more", "improvement maintained for 3 years", "after two years everything is satisfactory", "no hint of a relapse for over 3 years", "3 years later now happily married", "no relapse over 5 years", "marriage perfectly happy", "looking forward to a very happy married life " (cases of impotence and frigidity). The book is pleasant reading, small enough to fit in one's pocket, could generally be read on a bus en route to work (even standing) and, believe it or not, provides a considerable amount of useful information.

W. HORSLEY GANTT

Peripheral Vascular Disease. By A. J. BARNETT AND J. R. E. FRASER. 219 pp., $9.50. Melbourne University Press, Melbourne, Australia. Also Cambridge University Press, New York, N. Y.

This book is shorter than most books on peripheral vascular disease and consequently can be read in a few hours by some one desiring a general idea about problems in this field. The material is organized ideally for a book of this type. Chapters are devoted to Physiology of Blood Vessels, Methods of Diagnosis, and Clinical Features of Peripheral Vascular Disease. Specific disease entities are discussed under each chapter heading but the primary division of the book is not by diseases. The chapter on physiology is especially enlightening in that it incorporates the recent work of A. C. Burton and others on the physics of smaller vessels and applies this to problems arising in disease. The authors' approach to diagnosis is a practical one based on sound physiological principles and stresses clinical manifestations rather than laboratory tests. Primary emphasis is placed on physiological diagnosis. For example, "Excessive Vasoconstriction" and "Excessive Vasodilatation" are considered and under each heading the diseases which can produce these physiological changes are described. The discussion of treatment is likewise based on a consideration of the physiological deficit.

Laboratory measurements are described and their limitations outlined. Venous occlusion plethysmography, a procedure with which the authors are familiar, is described in some detail. The book serves as an excellent introduction to the subject of peripheral vascular disease and will represent a handy guide to diagnosis and treatment for those not commonly concerned with these conditions. It is not as comprehensive as the larger, more familiar books, but has an excellent up-to-date bibliography.

RICHARD S. ROSS

Tumor-Host Studies, The Physiological and Pharmacological Action of an Iodide-trapping Substance Formed in Tumor-bearing Animals. By KENNETH G. SCOTT AND CHIN-TZU PENG, University of California Publications in Pharmacology, volume 2, no. 22. pp. 345–376, 75 centrs. University of California Press, Berkeley, California

This booklet is a presentation of experimental work. In tumor-bearing rats an expansion of the total iodide pool of the body occurs, as shown by measurements employing radioiodine. In addition, the tumor (a fibrosarcoma) contained measurable amounts of radioiodine, and the skin over and near the tumor contained greater quantities of radioiodine than skin remote from the tumor. The studies were expanded to investigate the importance of the size of the tumor on this effect, the nature of the iodide compounds within the tumor, and the inhibitory effect of one tumor transplant upon another. The mechanism of this iodide-trapping effect in cancerous rats is not established, but the phenomenon is of interest

SAMUEL P. ASPER, JR.

Diabetes Mellitus: Objectives and Methods of Treatment. (American Lecture Series). By HENRY T. RICKETTS. 123 pp., $3.25. Charles C. Thomas, Springfield, Illinois.

This monograph, intended primarily for the general practitioner, consists largely of material which has appeared previously in various journals, and represents current practice in diabetic management at the University of Chicago Clinics.

A brief initial section concerns the diagnosis of diabetes mellitus. Subsequently general management with diet and insulin preparations, and handling of acidosis and during surgical procedures are discussed in detail. Proper patient education and detection of complications are stressed. Finally, modified American Diabetes Association material on the calculation of diets is presented.

The publication date was apparently too early to permit discussion of the Lente insulins. Otherwise, the material is current, accurate, and well-presented and should be quite useful to the practitioner outside the hospital. Its value to the house officer is qualified to the extent that certain details, perhaps inappropriate to nursing and dietetic routines at some hospitals, might require modification. Any scheme for managing diabetes is subject to some criticism of detail by advocates of various techniques of management. In the way of presenting a satisfactory general approach and stressing attention to the many important facets of diabetic care this monograph is above reproach.

GORDON CADER

An Autumn Gleaning. Occasional Letters and Addresses. By SIR HENRY HALLETT DALE. 225 pp., $4.25. Interscience Publishers, Inc., New York, N. Y.

In this volume, the author reflects upon the progress of natural science and of medical research in particular from the time of Harvey to the present. As he states in his introduction, he was too busy with his own researches during his more active life to lecture, so that most of the addresses included were delivered on commemorative occasions during the last decade. Thus they represent the philosophical reflections of a truly great scientist as he reviews the

development of his own field of endeavor, to which he has contributed so much. To his own accomplishments he sparingly and modestly refers. For those of others he is very unstinted in his praise, and weaves their contributions into an ever expanding pattern of increasing knowledge of the anatomy and physiology of the human body and the ills that beset it. His style is elegant, and he writes in the manner to which he refers when speaking of Benjamin Franklin's writings: "with that terse economy of words which marks the style of those who know the use of our English language at its noble best."

The author leaves no doubt in the mind of his reader that the tremendous advances in medical science are attributable to the use of experimentation in research. In his discussion of Accidents and Opportunism in Medical Research, he makes it quite clear that accidents in research are observations of a keen and open mind, always inquiring in its attitude toward unexpected results in experiment. These, when pursued, often eventually unfold their true meaning. This is vastly different from relying upon chance observation for one's inspiration. This bespeaks the genuine search for truth in research which the author himself so ably represents, and which is found only in clear and imaginative thinking and after hard and well thought-out work.

The nobility of scientific research as a way of life is a deep conviction of the author, and the mental discipline developed by accurate observation and careful interpretation create in one so dedicated a depth of knowledge which is culture in itself. Such else as is desirable for broad culture is a natural sequel to such training and is acquired by contact with the intellectual pursuits of others in a university atmosphere. Whereas he has great respect for tradition and the achievements of those who have gone before, he is not so steeped in the past as to be in any sense rigid. He is able to blend his wholesome respect for tradition with the ever expanding vista of the future to create a harmony of intellectual maturity, with all of its stability, and at the same time retain the enthusiasm and eagerness of youth which the challenge of the unknown presents to the inquiring mind in its search for truth. Medical research has done as much for the author and his philosophical reflections upon the accomplishments of his generation in medical science, with the most sparing reference to his own contributions to that development, should be an inspiration to all who truly care to add to the sum-total of human knowledge in whatever sphere their interests may lie. *An Autumn Gleaning* should have an appeal to scientific and non-scientific minds alike, and contains only two essays of a truly scientific nature. It is to be commended to all who would enjoy the development of the experimental approach to medicine as told by one who has played a prominent role in this era in medical science, which continues to hold and present almost limitless possibilities.

CHARLES W. WAINWRIGHT

Operative Orthopedic Clinics. By LEWIS COZEN AND ALVIA BROCKWAY in collaboration with PAUL E. MCMASTER. 329 pp., $10.00. J. B. Lippincott Co., Philadelphia, Pa.

This book, not intended as a text, is a compilation of the commonly employed orthopedic surgical procedures practiced by the authors in two busy clinics. Much information in a concise form is available with most of the procedures time honored ones, proven sufficiently satisfactory to the authors to be considered routine for the problems at hand.

The work is well prepared in a regional manner, with individual chapters for the surgical treatment of fractures and some selective plastic procedures. Little if any alteration of the original techniques has been made by the authors, though many of the procedures are described too meagerly. However, a very excellent bibliography enhances the value of the book, and all of the procedures are accompanied with interesting "remarks," the authors discussing errors and pitfalls, as well as the merits of the operations. There are numerous illustrations, all line drawings, but extremely well done.

The book should be of particular interest and value to trainees in orthopedic surgery, as well as a desirable addition and ready reference to the library of anyone interested in orthopedics.

H. Alvan Jones

Color Atlas of Pathology. Vol. II. Prepared under the auspices of the U. S. Naval Medical School of the National Naval Medical Center, Bethesda, Md. 450 pp., $20.00. J. B. Lippincott Co., Philadelphia, Pa.

The second volume of the Color Atlas of Pathology covers the endocrine system, including pituitary, thyroid, parathyroid, adrenals and pancreas; gynecology and obstetrics, including reproductive organs; breasts; male genital tract; and skin. At the beginning of each section there is a brief discussion devoting a paragraph to each main item in the field covered. This is followed by brief case histories and short descriptions of the colored gross and microscopic pictures. The technical quality of the colored reproductions, of which there are many, is good.

Certainly the Atlas would not take the place of fresh gross specimens and microscopic slides nor of a textbook such as Anderson's combined with collateral reading, either for the second-year pathology student or for the clinician. However if adequate fresh material and suitable slides are not avai'able, or as a supplement, the Atlas could be useful.

For physicians in other fields the three-volume series would provide a broad and yet condensed survey of gross and microscopic pathology.

O. M. Wilbur, Jr.

BOOKS RECEIVED FOR REVIEW

Bacterial Anatomy. The Sixth Symposium of The Society for General Microbiology. Edited by E. T. C. Spooner and B. A. D. Stocker. 362 pp., $6.00. Cambridge University Press, New York, N. Y.

Clinical Recognition and Management of Disturbances of Body Fluids. 2nd Edition. By John H. Bland. 522 pp., $11.50. W. B. Saunders Co., Phi'adelphia, Pa.

Collagen Diseases, Vol. II. By John H. Talbott and R. Moleres Ferrandis. 232 pp., $6.50. Grune & Stratton, Inc., New York, N. Y.

Color Atlas of Oral Pathology. Prepared under the auspices of the U. S. Naval Dental School of the National Naval Medical Center, Bethesda, Maryland. 188 pp., $12.00. J. B. Lippincott Co., Philadelphia, Pa.

Cybernetics. Transactions of the Tenth Conference, April 22, 23, and 24, 1953. Edited by Heinz von Foerster. 100 pp., $2.75. The Josiah Macy, Jr. Foundation, New York, N. Y.

Die Septische Thrombophlebitis, Vol. II. By Fritz Felsenreich and A. Kristinsky. 94 pp., $2.88. Wilhelm Maudrich, Vienna, Austria. Also Intercontinental Medical Book Corp., New York, N. Y.

Electrocardiography. Fundamentals and Clinical Application, 2nd edition. By Louis Wolff. 342 pp., $7.00. W. B. Saunders Co., Philadelphia, Pa.

Gestation. Transactions of the Second Conference March 8, 9 and 10, 1955. Edited by Claude A. Villee. 262 pp., $5.00. The Josiah Macy, Jr. Foundation, New York, N. Y.

In the Doctor's Office. The Art of Being a Medical Assistant, 2nd edition. By Esther Jane Parsons. 326 pp., $3.95. J. B. Lippincott Co., Philadelphia, Pa.

The Inquisitive Physician. The Life and Times of George Richards Minot. By Francis M. Rackemann. 288 pp., $5.00. Harvard University Press, Cambridge, Mass.

Laboratory Tests in Common Use. By SOLOMON GARB. 160 pp., $2.00. Springer Publishing Co., Inc., New York, N. Y.

Midwifery. Principles and Practice for Pupil Midwives, Teacher Midwives and Obstetric Dressers, 4th edition. By R. CHRISTIE BROWN, BARTON GILBERT, DONALD B. FRASER AND RICHARD H. DOBBS. 892 pp., $5.00. Edward Arnold, Ltd., London, England. Distributed by The Williams & Wilkins Co., Baltimore, Md.

Technique of Operative Surgery. First Volume: Stomach-Duodenum. The Operations of the Billroth Type II. By RAIMUND WITTMOSER. 350 pp., $12.48. Wilhelm Maudrich, Vienna, Austria. Also Intercontinental Medical Book Corp., New York, N. Y.

Textbook of Medical Physiology. By ARTHUR C. GUYTON. 1030 pp., $13.50 W. B. Saunders Co., Philadelphia, Pa.